THE American Journal OF Gastroenterology

VOL. 25, NO. 4 APRIL, 1956

Third Annual Convention
New York, N. Y.
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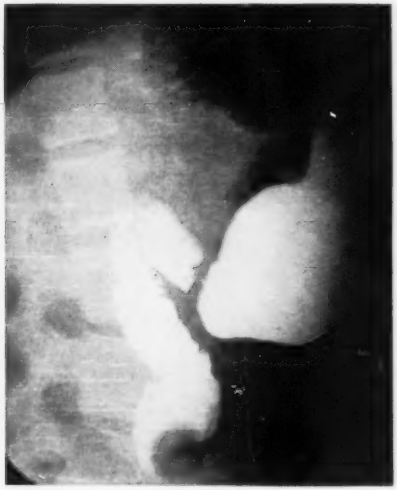

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VOL. 25, NO. 4 APRIL, 1956

The American Journal of Gastroenterology

(FORMERLY THE REVIEW OF GASTROENTEROLOGY)

The Pioneer Journal of Gastroenterology, Proctology and Allied Subjects in the United States and Canada

contents:

Owned and published monthly by the American College of Gastroenterology, Inc. Business Office: 33 West 60th St., New York 23, N. Y. Editorial Office: 146 Central Park West, New York 23, N. Y. Subscription rate, U. S. and possessions: One year $8.00, two years $14.00 (foreign $10.00, $18.00). Single copy: $.75. Reentered as second class matter at the Post Office at New York, N. Y., under the act of March 3, 1879.

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OFFICIAL PUBLICATION

of the

AMERICAN COLLEGE OF GASTROENTEROLOGY

33 West 60th Street, New York 23, N. Y.

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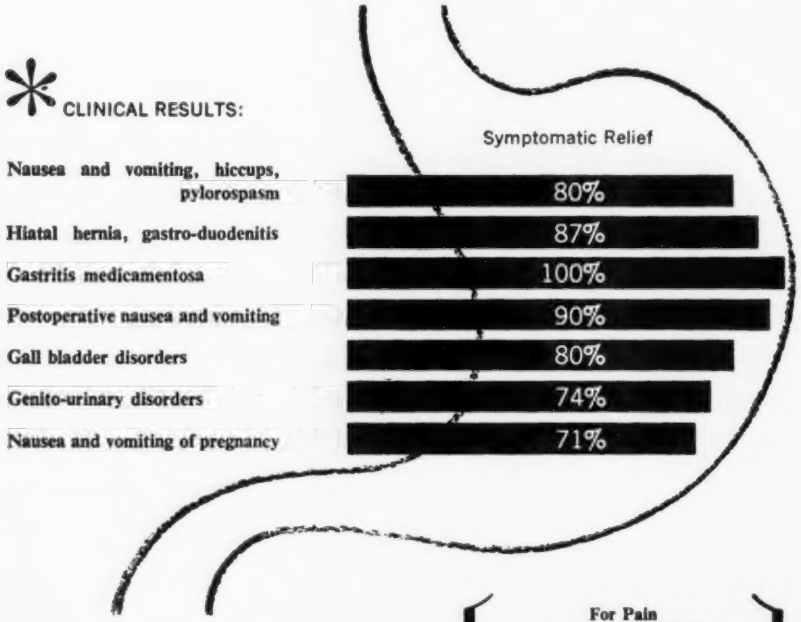

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THE American Journal OF Gastroenterology

A monthly journal of Gastroenterology, Proctology and Allied Subjects
(FORMERLY THE REVIEW OF GASTROENTEROLOGY)

VOLUME 25 APRIL, 1956 NUMBER 4

THE PATHOGENESIS AND THERAPY OF HUMAN AMEBIASIS*

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New Orleans, La.

At the present time there is no doubt that *Endameba histolytica* is or may become at any time a pathogenic parasite of man and may cause a certain percentage of acute and chronic cases of amebiasis. This parasitic ameba has been studied in man and in other animals and it has been grown in a variety of culture media, but never in pure culture in the complete absence of accompanying bacteria.

Infections with *E. histolytica* present many interesting and unsolved problems, with reference to the occurrence of clinical manifestations. The large majority of persons found infected with this parasite have no marked symptoms referable to the infection. There are a small number who develop mild intestinal symptoms and a very small proportion develop severe amebic dysentery. Although the incidence of amebiasis varies in different parts of the United States, the frequency of amebic infection of the bowel with hepatic complications is probably much greater than is commonly realized.

Surveys from all parts of the world have shown that among apparently healthy, normal individuals, a varying percentage harbor *E. histolytica* in their intestinal tract. The prevalence of the infection varies in different localities, but it is true that there exists throughout the entire world a great reservoir of amebic infection in individuals who appear to be normal, healthy and without apparent intestinal symptoms of the infection. Having such a large reservoir of infected individuals, it is interesting that there is so little correlation between the incidence of these healthy carriers and the number of cases of acute amebic dysentery in the individuals harboring the parasite.

Another interesting question which has never been answered is, when the symptomless carriers do develop acute amebic dysentery, is the pathology due

*Read before the Second Annual Convention of the American College of Gastroenterology, Chicago, Ill., 24, 25, 26 October 1955.
†Louisiana State University School of Medicine.

to the same strain of *E. histolytica* which had been present in the carrier state, or was the disease produced by a new infection or a different strain of the ameba. If the pathology was due to the original strain, then we must conclude that there has been some change in the intestinal tract or in the ameba which stimulated the parasite to produce massive tissue destruction.

Even though we now have a vast amount of information regarding the habits and life history of *E. histolytica* there are still wide gaps in our knowledge of the pathogenesis of this animal parasite. One of our main questions is why are there far greater numbers of symptomless carriers who pass only cysts and who are apparently asymptomatic than there are cases of acute amebic dysentery? This question of the symptomless carrier is one of peculiar difficulty. In 1913 Walker and Sellards, working in Manila, Philippine Islands, fed *E. histolytica* cysts from healthy carriers, some of whom had never had signs or symptoms of the infection, to 16 healthy volunteers. Fifteen of the 16 fed cysts became infected with *E. histolytica*, but only 4 of the 15 subsequently developed acute amebic dysentery. The specific explanation for these clinical and pathological variations is not known. It may be related to the parasite itself, to the condition of the host, to possible nutritional factors, to environmental influences of various kinds or to a combination of one or more of these factors.

One of the difficult questions to clarify is the condition of the mucosa in the symptomless carrier of *E. histolytica*. It has been found repeatedly that some amebic ulceration of the large intestine of man, and often amebic liver abscess, may occur in individuals who have had no signs, symptoms, or other evidence of amebic infection. Are there cases of known amebic infection in whom no ulceration is ever present? In an attempt to find some information on this point, Faust in 1941, examined the intestinal tract of 202 persons within four hours after death by accident. Of the 202 individuals, 13 were found to harbor *E. histolytica* in the large intestine. In 7 of the 13 positives superficial lesions of varying extent were found. In 6 others no lesions could be found throughout the entire length of the large intestine. In 2 of the 6, infection was established by the finding of a single typical *E. histolytica* cyst in each case. This study indicates that there may be an extensive amebic infection in the large intestine without any gross evidence of tissue pathology.

Frye and Meleney, 1938, infected several rhesus monkeys with a human strain of *E. histolytica* which had been found highly pathogenic for kittens. In one monkey the infection persisted for several months and trophozoites were always abundant in the stools but there was no evidence of dysentery or of even mild tissue damage. The animal was sacrificed after several months of continuous observation and the entire intestine examined carefully. No gross lesions were found although numerous active trophozoites were found in all portions of the large intestine. Blocks were fixed and sections from numerous

areas showed amebae in the lumen, on the surface of the mucosa and in the crypts of the glands but there was no penetration or evidence of damage to the adjacent epithelial cells. Another monkey infected with the same strain of *E. histolytica* became emaciated and appeared chronically ill several weeks after infection was established. There were numerous amebae in the stools but no frank dysentery. The animal was sacrificed a few weeks after becoming ill and several well defined amebic lesions were found in the area of the cecum. The animal also had far advanced pulmonary tuberculosis which was the primary cause of the chronic illness. This seems to indicate that chronic illness and debility of any nature may break down the balance between host and parasite.

The pathogenicity of various strains of *E. histolytica* have been studied by many investigators. Meleney and Frye, over a ten-year period from 1931 to 1941, studied the pathogenicity of a number of strains of *E. histolytica* in kittens. This work was planned with the dual purpose of comparing the severity of the lesions produced by the different strains and of observing the effect of continuous, prolonged cultivation *in vitro* on the pathogenicity of the strains. It was necessary to develop a practical method of studying the pathogenic activity of the various strains and be able to compare each strain under uniform conditions.

In the pathogenicity studies all precautions were taken to prevent the introduction of new bacteria into the cultures. Interchanging the bacterial flora between our more pathogenic and less pathogenic strains had no apparent effect upon the pathogenic activity of the amebae. It was found that variations in the suspending media employed in the inoculation of cultures of *E. histolytica* into kittens did affect the pathogenic activity of the amebae. These controlled pathogenicity studies, using a standard number of experimental animals in each series, showed that there were differences in the ability of these strains to produce pathology in kittens and that this difference could be demonstrated and was constant over a period of years. It was also demonstrated in these pathogenicity studies that with the strains of *E. histolytica* and kittens which we employed, no strain proved to be nonpathogenic and only one of several strains showed a consistent decrease in pathogenic activity as a result of artificial cultivation.

The small and large races of *E. histolytica* have been considered by some to account for differences in clinical manifestations. Some consider the small race much less pathogenic than the large race. Frye and Meleney, 1938, established a small race of *E. histolytica* in culture from a patient with mild gastrointestinal tract symptoms and tested the pathogenicity of this strain in a series of kittens. Cultures of this strain were inoculated into 22 kittens and 5 became infected. The lesions in these animals were superficial, there being little tendency for the amebae to penetrate deep into the tissues as was true of

almost all of the large strains of amebae which were studied in kittens. It is not possible to transfer this information from the kitten directly to the human but it does indicate that in infection with the small race of *E. histolytica* there may be only superficial lesions and that with infections with this type of ameba in man there would be no signs of symptoms of the disease.

In a recent report by Jones, Cassis, Floyd and Mansour (1955), evidence of a difference between the clinical manifestations in patients harboring large and small race *E. histolytica* was presented. They studied 19 "apparently healthy" Egyptian employees for a period of 24 weeks before treatment was given. The patients were studied carefully and then treated. Posttreatment examinations were made again during a 24-week follow-up period, including a control group of patients with no infection. The findings in this controlled linear study of nondysenteric and mild hepatic forms of amebiasis in Egyptians were interpreted as clinical support for the concept of mild pathogenicity of the small race and for the concept that "apparently healthy carriers" of either race may have mild signs and symptoms if followed serially over a long enough period of time.

Pathogenesis of Amebiasis

We are all aware of the fact that infection with *E. histolytica* presents many interesting problems regarding the occurrence of tissue pathology and the accompanying clinical manifestations of the disease. In order to understand the possibilities we must have a general understanding of the life history and other activities of this parasite.

Infection occurs by the introduction into an uninfected host a cyst or cysts into the mouth. The cyst of *E. histolytica* passes unharmed through the stomach and into the small intestine. During its passage through the small intestine or after arrival in the cecum, the four nucleate ameba within the cyst becomes active and emerges from the cyst.

After excystation, the normal four nucleated ameba undergoes further nuclear division and single nuclei, with a portion of ectoplasm, separate into eight small motile amebae. This process of multiplication takes place in the lumen of the cecum. Here the amebae grow to full size, and then undergo mitotic and cellular division. The amebae from the cecum may be carried in the fecal contents toward the terminal portion of the colon, undergoing encystation in preparation for survival outside the body until they are ingested by a new host. If conditions in the cecum or parts of the large intestine are favorable for tissue invasion the motile amebae may penetrate the wall of the intestine and produce lesions. The amebae may produce tissue destruction on the surface of the mucosa, in the natural depressions, or rugae; or in the lumen of the glands.

The penetration into the tissues may be accomplished by combined physical and chemical action. Ameboid movement of the parasite may permit penetration between epithelial cells, or the lytic toxin of the amebae may digest these cells before penetration into the deeper tissues takes place. Frequently the amebae penetrate beneath the epithelial cells to the base of the glands and there multiply, outside the basement membrane, before progressing into the connective tissue stroma between the glands. From here they pass down toward the *muscularis mucosae*, causing edema and necrosis of the tissue and dilatation, rupture or thrombosis of capillaries. Ultimately the necrosis involves the entire thickness of the mucosa. It may extend laterally over a wide area, or it may be sharply limited to a small group of glands. The amebae in the fundi of the glands soon break through the basement membrane and penetrate the *muscularis mucosae* either through the tissue spaces or in the lymph or blood vessels.

In the submucosa the amebae spread out in all directions between the connective tissue fibers. Their toxin causes edema, fibrin formation and degeneration of cells and intercellular fibers. The submucosa often becomes several times its normal thickness. There is little or no cellular response on the part of the host to the amebae, so that in early lesions before bacterial contamination few polymorphonuclear leucocytes and only a moderate number of mononuclear cells may be found in the lesions. With progression of the lesions due to the amebae the bacteria gain access to the tissues, followed by a marked polymorphonuclear response and the degenerating submucosal lesion takes on the appearance of a pyogenic abscess. At the periphery of such a lesion, bacteria are usually absent, but numerous amebae are present in the advancing area of edema and necrosis. The development of lesions in the submucosa leads to interference with the nutrition of the mucosa above it and the formation of the typical ulcer with overhanging edges, with extrusion of blood, necrotic material and amebae into the lumen of the intestine. Advancing beyond the area of necrosis, the amebae in the submucosa may enter the lymph or blood vessels, or may penetrate into other layers of the intestinal wall. If they enter blood vessels, they are carried by the blood stream to the liver, where they may form emboli with necrosis of the capillary walls and with continued multiplication and necrosis there eventually forms an amebic liver abscess.

The process that has been described represents the unobstructed development of the severest type of amebic lesion in the large intestine of man. The lesions are as a rule most numerous in the cecum, proximal ascending colon and the rectosigmoid region. As has been stated, we often find, in persons dying from other causes than amebiasis, no gross evidence of amebic lesions, but microscopic lesions may be found in tissue sections. In such lesions there may be no definite necrosis of the tissues. The glandular epithelium may be missing in small areas, but except for the presence of *E. histolytica* trophozoites there is little or no change in the surrounding tissue. Such a condition

either represents the presence of a strain of *E. histolytica* of a low degree of pathogenicity or great resistance to the parasite on the part of the host. This is without question the condition that exists in some of the cases of amebiasis that produce no clinical symptoms.

Extraintestinal Amebiasis

Extraintestinal lesions are metastatic, coming primarily from the intestinal lesions. These lesions in other parts of the body may develop in the absence of any intestinal symptoms of the infection. The most common and important of the complications of amebiasis is amebic hepatitis or amebic abscess of the liver. The amebae are transported from the intestinal lesions to the liver by way of the portal blood stream. With superficial localization of the amebic liver abscess its extension to the surface of the liver is the rule, and adhesion to the adjacent viscera or parietal peritoneum is common, often resulting in perforation or direct extension outside the liver. Although the incidence of amebiasis varies in different areas, the frequency of amebic infection of the bowel and its hepatic complications are probably much greater than is commonly realized.

The next most common site of extraintestinal amebiasis is the lung. Such lesions may occasionally be embolic in origin but are usually caused by direct extension of liver abscesses through the diaphragm. The abscess may rupture into the pleural or pericardial cavity, but more often the lung becomes adherent to the diaphragm and extension occurs directly into the lower lobe. With the advance of the amebae into the lung, a localized pneumonia develops with rapid formation of an abscess. Such an abscess contains the material typical of amebic lesions. At the periphery of the abscess is a pneumonic process, partly interstitial in character but mainly showing the alveoli filled with fibrin and amorphous material containing few cells. Numerous amebae may be irregularly distributed in the alveoli and to a lesser extent in the interstitial tissue.

The lung abscess usually opens into a large bronchus, discharging in the sputum a brownish mucoid material containing blood and amebae. If there is a direct connection with the liver, the discharge is similar to that of a liver abscess.

Amebic lesions of the skin and subcutaneous tissues are also frequently encountered. Such lesions may occur after surgical drainage of an amebic liver abscess, after drainage of a ruptured appendix of ruptured ulcer of the colon, from a colostomy opening or from direct extension of rectal ulcers through the anus by way of a fistula. They would probably never occur if the primary condition was recognized as amebic and drug treatment instituted.

Other extraintestinal amebic lesions have been reported, but these are extremely rare. Amebic abscesses of the brain are usually secondary to liver

and lung abscesses. Amebic infections of the gallbladder and various areas of the genitourinary tract have been described. When *E. histolytica* are found in these areas it is undoubtedly due to an extension from a primary site in the liver, in the case of the gallbladder, or from the colon in cases of genitourinary tract involvement. These complications are extremely rare but must be kept in mind as a possibility in differential diagnosis.

TABLE I

AGENTS USED IN THE TREATMENT OF AMEBIASIS

I. *Cephaline Alkaloids*
   1. Emetine hydrochloride
   2. Emetine Bismuth Iodide
      (20% Emetine—20% Bismuth administered orally)

II. *Halogenated Hydroxyquinolines*
   1. Chiniofon (Yatren-Anayodin) (28% Iodine)
   2. Diiodoquin (63.9% Iodine)
   3. Iodochlorohydroxyquine (vioform) (37.5% Iodine)

III. *Arsonic Acid Derivatives*
   1. Acetarsone (Stovarsol) (27.3% metallic arsenic)
   2. Carbarsone (28.5% metallic arsenic)
   3. Thiocarbonate (Thioarsenite)
   4. Bismuth glycolgarsamilate (Milibis)
      (15.01% metallic arsenic—41.88% metallic bismuth)

IV. *4-Aminoquinolines*
   1. Chloroquine phosphate (Aralen et al)
      Diphosphate dihydrate (62% base) administered orally
      Hydrochloride (89% base) administered parenterally

V. *Antibiotics*
   1. Terramycin
   2. Aureomycin
   3. Others

DIAGNOSIS OF AMEBIASIS

The laboratory diagnosis of amebiasis is not particularly difficult if a few simple fundamental procedures are observed. The diagnosis of amebiasis, as with other technical procedures, requires some knowledge of the biology of the parasite and broad experience in identification and differentiation of the nonpathogenic amebae which may be found in the intestinal tract of man.

The clinical diagnosis of intestinal amebiasis is not difficult to confirm by laboratory technics. Specific diagnosis rests essentially upon demonstration of either cysts or trophozoites of *E. histolytica*. Insofar as is practicable, the

procedures designed to demonstrate this animal parasite should be exhausted before accepting a clinical or a therapeutic diagnosis of amebiasis.

Swartzwelder in 1952, pointed out that errors in the diagnosis of amebiasis are of three kinds: 1. failure, because of poor technic or inadequate search, to detect the organism in individuals who harbor the parasite; 2. confusion of various nonparasitic objects in the stool or in sigmoidoscopic aspirate with *E. histolytica;* and 3. confusion of other intestinal protozoa with this pathogen.

Sigmoidoscopic examination is a particularly valuable adjunct to stool examination, but this procedure has limitations. In a high percentage of patients with intestinal infection the lesions are beyond the range of this instrument and many cases of amebiasis would be overlooked if this method of diagnosis were relied upon entirely for diagnosis. This would apply particularly to patients with lesions confined to the cecum, appendix and ascending colon, which are sites of frequent involvement without lesions being present in the lower portion of the large intestine.

The complement-fixation test for amebiasis has not yet been placed on a sufficiently dependable foundation for general use in diagnosis of amebiasis.

Therapy of Amebiasis

In our description of the life history and pathogenesis of *E. histolytica* it was pointed out that the trophozoites may live and multiply in the lumen of the intestine, in the wall of the bowel or in the tissues in other parts of the body. In the treatment of amebiasis, the drugs to be used must be so selected that they exert their action in the right place. At the present time we have a number of drugs which are recommended for the treatment of amebiasis, and various of these drugs have their individual proponents. Among the old standard amebacides, emetine is the only effective systemic drug. The other drugs act locally in the lumen of the intestine and are not effective in the elimination of the tissue parasites. With the introduction of the antibiotics, and particularly the broad-spectrum antibiotics, it was soon learned that they were effective in clearing a large proportion of lumen and tissue infections in the wall of the intestine but the antibiotics are of no value in the prevention or treatment of extraintestinal amebiasis.

The drugs most successful for the treatment and control of amebic infection are those having a sufficient margin of safety to permit their use without danger to the host and yet are capable of relieving the patient of symptoms and eradicating the causative agent, *E. histolytica.*

Table I shows the drugs now commonly used in the treatment of amebiasis.

The ideal amebacide should be absorbed and distributed in its active form so that it is effective systemically against trophozoites in the tissues as well as

against motile forms in the lumen of the intestine. With the introduction of antibiotics their efficiency in the treatment of amebiasis was studied. Hargreaves, in 1945, reported that 57 patients with resistant amebiasis showed marked improvement when treated with penicillin. He found that the temperature of these patients usually became normal within 24 hours. The stools in most instances became normal within 48 hours, but the amebae were still present.

Shaffer and Frye, 1947, showed that penicillin and streptomycin, alone or combined, in fairly high concentrations, when added to cultures of *E. histolytica*, had little if any effect on the growth and multiplication of the amebae, but did inhibit growth of certain bacteria in the cultures. Armstrong, Wilmot, and Elsdon-Dew in 1949, observed partial or complete healing of amebic ulcers, demonstrable by proctoscopic examination, following treatment with penicillin and sulfasuxidine.

TABLE II

RESULTS OF TREATMENT OF ACUTE AMEBIC DYSENTERY WITH THREE BROAD-SPECTRUM ANTIBIOTICS ASSESSED AT THE END OF SIX WEEKS

Therapy	Number of Patients Treated	Success		Failure	
		Number	Per cent	Number	Per cent
Terramycin	40	39	97.5	1	2.5
Aureomycin	41	29	70.7	12	29.3
Chloromycetin	39	21	53.8	18	46.2

From: Frye, Brooke and Weinstein. Ann. New York Acad. Sc., **53**:1104, 1952.

In contrast to penicillin and streptomycin, bacitracin, when added to cultures of *E. histolytica* inhibited growth of the amebae. Longacre in 1948, treated several patients with amebic colitis with bacitracin given orally. The amebae disappeared from the stools, the lesions cleared rapidly and there was rapid clinical improvement.

Clinical successes using aureomycin in the treatment of amebiasis was first reported by McVay and his associates in 1949. In 1950, Armstrong, Wilmot and Elsdon-Dew reported the use of aureomycin in acute cases of amebic dysentery.

Terramycin was developed in 1950. Most and van Assendelft, 1950, found terramycin effective in the treatment of intestinal amebiasis. Killough and Magill in 1951, reported the treatment of seven patients with amebic dysentery with terramycin. In all patients there was disappearance of bloody diarrhea, tenesmus, and other dysenteric symptoms within two to six days. Stools and proctoscopic specimens became negative for amebae after 2 days in four

patients. In one patient, an amebic abscess of the liver developed during terramycin therapy.

Tobie et al in 1951, treated all occupants in separate buildings of a mental institution using bacitracin, aureomycin or terramycin; a single drug was used in each building. Though all patients were asymptomatic prior to therapy, 49 per cent harbored *E. histolytica.* Terramycin was found to be 100 per cent effective in eliminating the organism from the intestinal tract on the basis of a six-month follow-up, aureomycin was 60 per cent effective and bacitracin only 28 per cent effective after 2.5 months of follow-up.

Armstrong, Wilmot and Elsdon-Dew in 1950, treated 52 African cases of acute amebic dysentery with aureomycin. This broad-spectrum antibiotic was given orally in doses of 0.25 gm. four times daily at 6 hour intervals for 15 days. Sigmoidoscopy was done daily until all ulcers were healed. The authors considered the successes with aureomycin, after 20 days, as 94 per cent against 50 per cent successes with emetine. They were disappointed, however, with the 14 per cent relapse rate among a small number of their "successful" aureomycin-treated cases who were followed for an additional 4 weeks after discharge from the hospital. These same workers used 1 gm. of terramycin daily for 15 days in 49 acute cases of amebic dysentery. At the end of 27 days there was success in 91.4 per cent of cases treated. Two patients developed hepatitis which progressed in spite of continued terramycin therapy and necessitated the use of emetine on the 16th day in one case and chloroquine on the 6th day in a second. They also used chloramphenicol, neomycin, streptomycin, bacitracin and certain combinations of antibiotics and other amebacides. From these studies they concluded that terramycin and aureomycin were very effective when used alone in acute amebiasis.

Frye, Brooke and Weinstein, 1952, gave a preliminary report of a comparative study of the efficacy of aureomycin, terramycin and chloramphenicol against acute amebic dysentery occurring in the United Nations' prisoners of war in Korea in 1951. The criteria for acceptance in the amebic dysentery study series were the presence of diarrheal disease with mucosanguineous exudate in the stools, visualized enteric lesions, and the presence of trophozoites of *E. histolytica.* No asymptomatic carriers were included in these studies.

In this study the same treatment schedule was used for all three antibiotics. Each patient received 2.0 gm. of the antibiotics as a loading dose and then 0.5 gm. every 6 hours for 10 days. After 10 days, treatment was stopped and the patients followed for a period of 6 weeks. The results obtained with these three antibiotics are shown in Table II. Terramycin in this group of patients was the most effective with only 1 failure or 97.5 per cent effective, aureomycin was less effective with 12 failures or 70.7 per cent effective and chloromycetin was least effective of the three broad-spectrum antibiotics with

18 failures or 53.8 per cent effective. There were surprisingly few gastrointestinal side reactions to these antibiotics among this group of patients.

Martin et al in 1953, reported on the complete study, in the prisoner of war camp, of the comparative efficacy of amebacides and antibiotics in acute amebic dysentery, used alone and in combination in 538 cases.

TABLE III

THERAPEUTIC RESPONSE IN 538 CASES OF ACUTE AMEBIC DYSENTERY ASSESSED AT END OF SIX WEEKS

Treatment Agent	No. of Cases	Therapeutic Response		Number Re-treated Before 6 Wk.	Failures followed for 6 Wk.		
		Success	Failure		Number with *E. histolytica* in Stools at 6 Wk.	Number Clinically Ill	Number with active Colitis Sigmoidoscopically
Standard Amebacides							
Emetine	22	10	12	2	10	1	1
Carbarsone	22	4	18	12	6	2	3
Chiniofon	24	9	15	6	9	1	1
Chloroquine	31	13	18	5	13	6	5
Emetine, carbarsone and chiniofon	23	19	4	0	4	0	0
Milibis-Aralen	22	11	11	4	7	3	0
Antibiotics							
Terramycin	104	98	6	3	3	2	3
Aureomycin	41	31	10	3	7	4	2
Chloramphenicol	41	11	30	9	21	10	13
Antibiotics and Amebacides combined							
Terramycin and standard amebacides for 10 days	97	93	4	2	2	1	1
Terramycin and chloroquine for 5 days	22	20	2	1	1	1	1
Aureomycin and chloroquine for 10 days	23	23	0	0	0	0	0
Supportive Therapy							
Bed rest and nutritional supplements	66	11	55	39	16	8	11

From: Martin, Garfinkel, Brooke, Weinstein and Frye: J.A.M.A. **151**:1055, 1953.

Table III gives the results of this extensive study. Carbarsone, chiniofon, chloroquine and chloramphenicol used alone had minimal therapeutic effect in this disease. Emetine and aureomycin alone and the combination of bismuth glycolylarsenate and chloroquine diphosphate (Milibis®-Aralen®) gave a good initial response but a high relapse rate. Emetine, carbarsone and chiniofon combined gave an excellent initial response but a moderate relapse rate. Terramycin alone and in combination with other amebacides and the combination of aureomycin and chloroquine diphosphate all gave excellent responses and low relapse rates.

Table III also shows the results obtained in a group of patients followed with only supportive therapy. At the termination of the follow-up period 11 of the 66 patients had no clinical or parasitological evidence of amebic infection. These observations demonstrate that spontaneous recovery does occur and must be given consideration in the evaluation of any specific therapy.

McHardy and Frye in 1954, reviewed the literature on the use of antibiotics in the management of amebiasis. They found that of the broad-spectrum

TABLE IV

RESULTS OF SOUTH BEND DIAGNOSTIC PROGRAM

Number of plant employees	1,561
Number of employees interviewed	1,548
Employees contributing specimens for examination	1,542
Percentage of employees harboring *E. histolytica*	52.4

antibiotic terramycin is the drug of choice in the management of amebiasis. Fumagillin (Fumadil), a direct-acting antibiotic, because of its restricted bacterial spectrum, is an efficient amebacidal substance. They also found that antibiotics were of no value as an amebacide in the treatment of extracolonic amebic involvements.

In a recent study Sappenfield et al in 1953, used terramycin and fumagillin in the treatment of a large group of individuals involved in a water-borne outbreak of amebiasis. The epidemic was confined to the employees of a woodworking plant. Stool specimens were obtained from all the employees and examined for *E. histolytica* and other intestinal parasites. The examinations were repeated on each individual until a diagnosis of amebiasis was made or until 4 negative specimens had been submitted. Table IV shows the results of the diagnostic program. There were no gross signs or clinical symptoms in any of the individuals harboring *E. histolytica* and all were working regularly. A mass treatment program was arranged in the plant with the approval of all concerned, including the individual, the private physician, local medical society,

plant management, the union and the health department. A treatment schedule was arranged so that one-half the daily medication was given in the morning in a treatment center set up in the plant. The other half of the daily dose was given to the patient each day to take just before leaving the plant at the close of the work day.

Infected individuals were treated with fumagillin, 20 mg. twice daily for 10 days, or terramycin, 1 gm. twice daily for 10 days. The type of treatment to be given to each individual was decided by alternately selecting cases as they arrived for their first day of therapy. A total of 805 employees reported for treatment. Terramycin was given to 405 and fumagillin to 400. After a complete analysis of the records, 714 employees had fulfilled one of the following criteria and were included in the final evaluation: 1. a positive stool

TABLE V

Results of South Bend Treatment Program

	First course of treatment			Second course of treatment			Total Treated	Total Negative	
	Number Treated	Posttreatment stool exam.		Number Treated	Posttreatment stool exam.				
		Neg.	Pos.		Neg.	Pos.		No.	Per cent
Terramycin	358	338	20	20*	16	4	378	354	93.7
Fumagillin	356	334	22	13†	11	2	369	345	93.5
Total	714	672	42	33	27	6	747	699	

*Treated previously with fumagillin. The other 2 were followed by private physicians.
†Treated previously with terramycin. The other 7 were followed by private physicians.
From: Sappenfield, Carter, Culbertson, Brooke, Payne and Frye: J.A.M.A. **159**:1009, 1955.

examination after completion of treatment or 2. four negative stool examinations over a 3- to 4-month follow-up period after completion of treatment of the 714 patients meeting these requirements. Three hundred and fifty-eight received terramycin and 356 received fumagillin.

The results of therapy with these two antibiotics are shown in Table V. After one course of therapy with terramycin, 338, or 94.4 per cent of the individuals, were negative. Of those treated with fumagillin 334, or 93.4 per cent, were negative at the end of the follow-up period. There were 42 patients still positive after the first course of therapy. Each of these patients was treated again, this time with the alternate drug. Four of the 20 patients remaining positive after the original fumagillin therapy were still positive after retreatment with terramycin. Two of 13 patients remained positive after retreatment with fumagillin.

This study reconfirmed that terramycin is an effective agent in the treatment of asymptomatic amebiasis, and that fumagillin was equally effective in the same group of individuals but the side reactions were more severe. This type of infection with *E. histolytica,* or with mild symptoms, is the usual type of infection seen by the practicing physicians in the United States. As has been mentioned, extraintestinal amebiasis is not eliminated or prevented with the broad-spectrum antibiotics. It has now been over two years since this treatment program was completed and there have been no reports of liver abscess or other extraintestinal amebiasis in the 805 employees diagnosed and treated.

During the past year Frye, in unpublished studies in a large mental institution, has used several of the newer amebacides and antibiotics*. Table VI gives some preliminary results of this study. Tetracyn has given results equal to those obtained with terramycin in the treatment of asymptomatic intestinal

TABLE VI

THE EFFICACY OF TETRACYN AND STYLOMYCIN AGAINST ASYMPTOMATIC AMEBIASIS

Number Patients Positive for *E. histolytica*	Antibiotic Therapy	Dosage	Unfavorable Reactions To Therapy	2 Months Follow-up Therapeutic Response	
				Success	Failure
33	Stylomycin	500 mg. daily—6 days	None	29	5
34	Tetracyn	2 gm. daily—6 days	None	31	3

amebiasis. Stylomycin has also been found effective in asymptomatic and acute carrier cases and there have been no side reactions to this antibiotic in the dosages used. Larger doses than those shown in Table VI are now being used and we have had no untoward reactions to date.

TREATMENT OF EXTRAINTESTINAL AMEBIASIS

The standard therapy of amebic hepatitis and amebic abscess of the liver until recently consisted of emetine injections alone or combined with aspiration of the contents of the abscess. Before antibiotic therapy, to control secondary bacterial infection, open drainage of the abscess increased the mortality rate. The emetine treatment of amebic hepatitis and liver abscess is usually successful, but a less toxic drug has been needed for the treatment of extraintestinal

*The following drugs were supplied by the makers for use in this study: Tetracyn by Charles Pfizer and Co., Brooklyn, N. Y., and Stylomycin by Lederle Laboratories, Division of American Cyanamid Co., Pearl River, N. Y.

amebiasis. Conan in 1948, was the first to use chloroquine against amebic hepatitis. He shrewdly combined the observations that chloroquine is found in high concentrations in the liver when administered by mouth and that it was effective against another protozoan, malaria. With this information he tested the action of chloroquine against *E. histolytica in vitro* and showed this drug to be active against the trophozoites. Since Conan's first report a large number of patients with amebic hepatitis and hepatic abscess have been treated with chloroquine and the results have been uniformly good.

Frye et al, in unpublished data, treated nine cases of amebic hepatitis with chloroquine. Three of the nine had a definite liver abscess. Five received chloroquine alone with excellent therapeutic results. One case had some persisting symptoms while on chloroquine, but progressed to complete recovery when terramycin was added. Two cases of liver abscess were treated with chloroquine and terramycin and one with chloroquine and emetine. Though there was improvement in all three on drug therapy, complete recovery was delayed until the abscesses were drained. From these studies it was concluded that chloroquine is a highly effective therapeutic agent in the treatment of amebic hepatitis.

Conan originally used a priming dose of 0.3 gm. of the base twice daily for 2 days and a sustaining dose of 0.3 gm. daily for 12 days. Chloroquine diphosphate (aralen) is the form available on the market at present and the dose is 0.5 gm. twice daily for 12 days. Chloroquine has been successful in hepatic infections which emetine failed to cure; likewise, chloroquine failures should be treated with emetine.

Although emetine has been used successfully in the treatment of skin amebiasis there have been no reports to date of the use of chloroquine in such cases. The fact that chloroquine is concentrated far more greatly in the liver tissue than in other tissues might mean that it would not be effective in extra-intestinal amebiasis other than in the liver.

Comment

In this presentation attention has been called to some of the unsolved problems in human amebiasis. We are still unable to explain why *E. histolytica* produces severe tissue damage under some circumstances and no damage at all in others. Asymptomatic carrier cases occur far more commonly than infections with definite signs and symptoms of infection with *E. histolytica*. Pathogenicity studies have shown that there is a difference between certain strains of *E. histolytica* when studied in experimental animals. There is also some clinical evidence that the small race produces fewer clinical manifestations in humans, when patients are followed over a long period of time, than with the large race.

A review of the life cycle and the pathogenesis of *E. histolytica* has been described in an attempt to get a better understanding of the problems involved in therapy. The site of action of an amebacide in the acute case of amebic dysentery and in the asymptomatic carrier, or in the extraintestinal infection, must be understood if successful therapy is to be expected. On the basis of present knowledge, all infections in man with *E. histolytica* should be treated.

The evaluation of antiamebic drugs and the comparative effectiveness in each case presents a number of problems. The response to therapy in cases of acute amebic dysentery is quite different from those patients with mild symptoms or in the asymptomatic carrier.

The length of time that the patients are followed after completion of therapy is very important, as many drugs seem to produce an apparent cure for several days or weeks, yet when the patient is examined several weeks later, a high rate of parasitological and clinical relapse is found. Stool examination technic and careful follow-up procedures also have a considerable bearing on apparent cure rate. The laboratory diagnosis of amebiasis is not particularly difficult, but as with any other diagnostic procedures, it requires some knowledge and experience. Specific diagnosis rests essentially upon demonstration of either the cysts or trophozoites of *E. histolytica.*

In the treatment of acute amebic dysentery, we are faced with the need for prompt relief of symptoms as well as the complete eradication of the parasite. In mild and asymptomatic cases the treatment would seem to be much simpler. Here we have little or no tissue pathology in the intestinal tract but the parasite must be eliminated from both the tissue and the lumen. Although emetine has been used for over 40 years in the treatment of amebic dysentery, and for a number of years it was the only amebacide available, one must remember that it is a toxic drug. The cure rate with this drug and with all other amebacides now in use varies considerably.

During the past few years a number of antibiotics have proven to be of considerable value in the treatment of all forms of intestinal amebiasis. In the hands of a large group of investigators terramycin has been found to be the most effective in eliminating the parasite from the tissues and from the lumen of the large intestine. Of the broad-spectrum antibiotics now in use, terramycin is the drug of choice in the management of intestinal amebiasis.

It must be emphasized here that the antibiotics have no apparent effect on extraintestinal amebiasis, in fact amebic abscesses of the liver have developed in patients while on antibiotics, and in whom the intestinal involvement had been eliminated. The treatment of choice in hepatic amebiasis is now chloroquine diphosphate. In certain cases emetine may be necessary if chloroquine fails. For other types of extraintestinal infection with *E. histolytica* emetine must still be considered the drug of choice due to lack of information on the use of

chloroquine in the treatment of extraintestinal amebiasis other than hepatic involvement.

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INTRAABDOMINAL SYMPTOMS DUE TO ANEURYSMS*†

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Referral of cardiovascular symptoms to the abdomen is a common occurrence. The term "acute indigestion" has often been applied to attacks of angina pectoris, coronary artery occlusion or pericarditis. The gallbladder has been suspected when these, and other vascular abnormalities have simulated cholecystitis. The stomach and bowel are awarded an ample share of diagnostic tests and manipulations when their dysfunction is basically vascular. The diagnostic problems due to blood vessel disease are assuming prime importance in many fields of medical art. For this reason dissecting aneurysms of the aorta are emerging from an obscure realm of academic interest to one of clinical consideration. The ten following cases are therefore presented in the hope that they will help clarify the onset of some symptoms often referred to the abdomen.

These ten patients were seen at the Holy Cross and Loretto Hospitals, Chicago, Ill., during the years 1952 to 1955. There were nine males and one female in the group. Their ages varied from 56 to 78 years and all had advanced atherosclerosis. All of the patients had pain in the abdomen as a major complaint at some time in the course of the acute terminal episode of dissection of the aortic wall. Table I lists the pertinent facts of the illness of each patient.

This table, designed primarily to show the type and location of pain in dissecting aneurysms of the abdominal aorta, brings out the same type of severe pain and shock in most of these patients. In only two was there difficulty in examination due to obesity. Three of the patients were emaciated and hypotensive. Of these two had had gastric resections for peptic ulcers within two years of death. The third had had a gastrojejunostomy 22 years previously, had a duodenal ulcer two years later and was a "dyspeptic" semi-invalid. To add to his troubles he had a benign prostatic hyperplasia and a pyelonephritis (Case 9 of this series). The pain invariably was localized in a quadrant and radiation to the lumbar region was most common. Two of the patients, in addition had pain in the groin or in a leg and were unable to walk. In these instances dissection had progressed past the aortic bifurcation to the iliac arteries.

Bowel distention, visualized in the cecum and colon in three patients in x-ray studies, were present in all patients. Two of them took citrate of magnesia

*Read before the Second Annual Convention of the American College of Gastroenterology, Chicago, Ill., 24, 25, 26 October 1955.

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TABLE I

Patient	Sex	Age	Occupation	Symptoms	Diagnosis	Death
1	F	62	Housewife	Cramping pain L.U.Q. Sudden onset with a desire to defecate. B.P. 100/60 Tender mass in L.U.Q. Pt. in shock.	Retroperitoneal hemorrhage possibly due to rupture of aortic aneurysm.	16 hrs.
2	M	64	Credit Manager	Pain in chest and Fainting. B.P. 115/90 to 40/20. Shock. Abd. tender in R.L.Q. with swelling. Bowel hypoactive. Emesis every few hours.	Perforated aneurysm of abd. aorta. Coronary heart disease.	38 hrs.
3	M	72	Retired Clerk	Vomiting—at times. Bloody for two days. Tenderness over all abdomen. Pain and cyanosis of legs.	Perforated gastric ulcer with peritonitis.	32 hrs.
4	M	60	Clerk	Difficulty in breathing. Dizziness, cyanosis, nausea and vomiting. B.P. 90/55.	Coronary heart disease. Myocardial infarct.	72 hrs.
5	M	62	Weigher	Pain in the L.L.Q. Vomiting 1 day. Obese abdomen with guarding in L.L.Q. This man had pain in abdomen the evening before hospitalization. He felt "something burst" in abdomen.	Ruptured diverticulitis with localized peritonitis. Mesenteric thrombosis. Retroperitoneal hematoma.	15 days
6	M	56	Machinist	Pain abdomen 3 days. Felt something "break in abdomen" before admittance, and pain became intense. Abdominal pain 3 days. Constipation 3 days. Vertigo and general weakness 2 days. Tender in abdomen on examination mass in epigastrium. Pain in legs. (X-ray-Gaseous distention of colon. Possible aneurysm of abd. aorta.)	Ruptured Aneurysm of abdominal aorta.	17 hrs.

TABLE I (*continued*)

Patient	Sex	Age	Occupation	Symptoms	Diagnosis	Death
7	M	67	Priest	Abdominal pain L.L.Q. 2 days This patient had had previous myocardial infarction at age 60. He had complained of "colitis" for about 20 years.	Bowel obstruction Mesenteric Thrombosis.	12 hrs.
8	M	71	Mechanical Engineer	Vague pain in abdomen 36 hrs. before. Then had excruciating pain. Had exploratory laporotomy for tender rigid L.L.Q. Retroperitoneal hemorrhage found from iliac to renal arteries.	Mesenteric Thrombosis.	28 hrs.
9	M	64	Barber	Pain radiated from right lumbar to inguinal region and abdomen was distended. Patient operated upon for renal tumor. Huge hematoma found in right retroperitoneal region. Rupture site of abdominal aneurysm found near right renal artery.	Right retroperitoneal tumor. Right renal colic.	20 hrs.
10	M	76	Retired	Pain in L.U.Q. and radiating to lower back. Vomited several times and urinated "red" once. He felt "full of gas" and had no bowel movement for 3 days.	Bowel obstruction X-ray study showed a possible dissecting aneurysm of the abdominal aorta.	24 hrs.

and experienced considerable relief. Both of these patients had severe pain and shock respectively within three and five hours of their last bowel movement.

Temporary recovery from shock with a return of blood pressure to normal levels occurred in five patients. Each of these sought relief from abdominal distention by attempting to have a bowel movement. Three fainted in attempting to defecate. Two collapsed and failed to rally from shock. One of the latter apparently had external rupture of the aneurysm at this time. The other had extensive fresh dissection about the aortic bifurcation and right iliac artery just prior to external rupture. One man, 62 years of age, was in shock on entrance to the hosiptal and withstood an exploratory laporotomy on the second day. Because of spotty hemorrhages in the mesentery and small bowel, multiple emboli from a possible cardiac source seemed present. A large retroperitoneal

hematoma was also noted but a dissecting aneurysm was not diagnosed. On the fifth day this man had a sudden pain in the left hypogastric region, resembling that of his initial attack. Three days later he had an episode of emesis and shortly after this a good natural bowel movement. He seemed fairly comfortable until a week later when he again had severe left hypogastric pain, a hugely distended abdomen, and then went into shock and died.

The last patient had had myocardial infarction four years previously and at autopsy had recent coronary thrombosis with marked myocardial infarction. The clot in the descending branch of the left coronary artery was first, partly organized, and compatible with an age of about two weeks. This thrombosis apparently coincided with the initial abdominal pain, beginning of dissection in the aneurysm, and the first episode of attack. The clot within the dissected wall of the abdominal aorta was laminated in most of its extent and showed evidence of early organization. Tremendous natural reparative forces were apparent in this abdominal aorta and led to the surmise that healing occasionally occurs in such dissections. Organization of such a clot with the production of a second channel within the aortic wall has been repeatedly recorded.

The extent of dissection in the wall of the aorta in these patients was remarkable. The longest dissection extended from the distal part of the aortic arch to 5 cm. beyond the superior mesenteric artery. Blood had forced its way beneath the parietal pleura and lung hiluses and had separated the medial layer from the others for two-thirds of the dorsal circumference of the thoracic aorta. The lining of the abdominal aorta above the renal arteries formed a lax distorted inner tube entirely surrounded by blood in a layer from 1 mm. to 12 mm. thick. Rupture into the retroperitoneal space was 17 cm. distal to the primary rent in the aortic arch. The blood clots recovered outside the aorta weighed 1,400 gm. In contrast to this huge extravasation were two from large dissections from the renal arteries to the aortic bifurcation. Although 75 per cent of the aortic circumference was a blood lake, 3 mm. to 15 mm. deep, only 50 and 80 gm. of blood respectively, had seeped through minute tears in the adventitia into the retroperitoneal fat. One patient had a recent thrombosis of the left descending coronary artery and evidence of recent myocardial infarction. The other had marked coronary artery sclerosis, extensive myocardial fibrosis and a parietal aneurysm of the left ventricle.

The other patients generally followed a pattern of aortic dissection with rupture and retroperitoneal extravasation of 800 to 1,200 gm. Four patients perforated to the left and two to the right. The aortic intramural hematoma extended from upper levels near the diaphragm to the aortic bifurcation and in two patients along the iliac arteries. The atherosclerosis of the abdominal aorta was advanced in all of the patients and none had any features of syphilitic aortitis. The one patient who lived 15 days, showed attempts at organization of the intramural clot and the early stage of a secondary lumen.

Recently Lary and Davis[1] entered such a false channel during aortography, in a patient who had evidence of vascular obstruction of his right arm and leg. As a result, the abdominal aorta was unusually wide, and the clinically obstructed right iliac artery was visualized. Four days later the patient died from rupture of his aneurysm into the pericardial sac. At autopsy a fresh tubular dissection of the entire aorta was found to extend to and obstruct the right iliac artery. Shennan[2] summarized the course of events in dissecting aneurysms as follows: "The sac communicates with the original lumen through a rupture or ruptures of the inner layers of the wall, and though in a few cases it remains as a hematoma, it more usually ruptures either to the exterior or back into the lumen. In the latter event the symptoms may disappear and the patient recover with an additional endothelial lined channel through which blood circulates."

There are numerous old healed dissecting aneurysms recorded. Thus Shennan found 79 in his total of 300 aneurysms. Flaxman[3] found 16 old aneurysms in a series of 19. Twelve were further classified as silent. These had a gradual onset and symptoms and signs of heart failure. The condition was unsuspected in these patients clinically.

The formation of a secondary lumen or double-barrelled aorta, while constituting a temporary lease on life, carries certain inherent hazards. The new channel when distended with blood may considerably diminish the caliber of the aorta. Blood in the channel may also hamper pulsation in the aortic collateral vessels which must traverse the channel. The likelihood of imbalance in the circulation is apparent with hypertension above the zone of dissection and hypotension below this region. Hypertension, despite an appearance of shock, may be thus explained in patients suffering from acute dissection of the aorta. The shock and electrocardiographic features were reported in detail by Levinson[4] et al.

Appreciation of the importance of such hypertension in hastening rupture of the weakened aorta led Shaw[5] to perform a novel operation. His patient had total obstruction above the renal arteries because of a dissecting aneurysm. The surgical procedure consisted of evacuation of the clot from the aneurysm, fenestration of the internal wall of the aneurysm in the abdominal aorta with establishment of a double-barrelled aorta, and repair of the dissection distally. The patient lived for nine days and then died of uremia and with a recurrence of arterial obstruction.

Dissecting aneurysms of the abdominal aorta, which are the major concern of this report, have lent themselves to extensive resection. Removed segments have been replaced with accurately fitted homografts. Much of the work was previously summarized by Rukstinat[6]. The interesting evolution of vascular surgery was highlighted by a review by Nabatoff[7]. In this, reference is made to various methods of support for vessels involved by aneurysms. Wrapping with

polythene film or with film and dicetyl phosphate has been repeatedly attempted. Disappointing results have necessitated subsequent aortic resection and replacement by a homograph as reported by DeBakey and Cooley[8]. They found minimal fibrosis about such wrappings in two patients and indeed regarded the aneurysmal wall thinner in some places than when first wrapped. This observation substantiates the conclusions of Crawford and Levene[9] that medial thinning is an essential part of an atheroma. They contend that this process is an early and constant part of the atheromatous lesion. It represents a region comparable to a shallow aneurysm partially or completely filled by a plaque of intimal thickening. This is in contrast to the usual view that medial thinning is due to pressure atrophy by the overlying intimal plaque.

The most common arterial change associated with dissecting aneurysms is described as a medial necrosis. The condition was described by Wiesel[10] in the medial coats of large elastic and even small peripheral arteries. His patients were young nonsyphilitics who died shortly after the onset of fulminating acute infections. The weakened condition of the media in dissecting aneurysms, is shown by the extent of bloody disruption in this layer before perforation occurs either to the outside or back into the aortic lumen. Even where the latter occurs with formation of a double-barrelled aorta, the lining and wall of the false lumen soon became atheromatous. The latter fact was demonstrated by Weiss[11] and his associates in three patients.

Additional evidence of primary medial change in dissecting aneurysms has been uncovered recently by Ponseti and Baird[2] in their experiments with lathyrism in rats. This disorder occurs in men and domestic animals in conditions of famine or dietary fad where légumes form the major food components. Studies of scoliosis and diseases of the cartilage matrix were the primary aims of the experiments but 38 to 75 per cent of the rats died of dissecting aneurysms during the fifth to ninth weeks. The scoliosis could be arrested by a return to a balanced diet and healing occurred in deformed long bones. Scrotal and ventral herniae also developed in the affected animals. The depleted diet apparently produced a fault in ground substance resulting in mesodermal defects of a wide variety. This feature was studied in human autopsy material by Bean and Ponseti[13] who found x-ray evidence in 35 per cent of 20 patients of skeletal deformity associated with dissecting aneurysm. They further indicate that 41 per cent of 37 patients with Marfan's syndrome had dissecting aneurysm of the aorta. Another 9 per cent of this group had fusiform or saccular non-dissecting aneurysms, making an impressive total of 50 per cent of aortic lesions. Of the ten patients considered at present three were emaciated invalids who had had restricted diets for 2 to 20 years. They had suffered from peptic ulcers of the stomach or duodenum and two had been subjected to partial gastrectomy. Five of the patients were on partially restricted diets because of previous myocardial infarction which had been studied in electrocardiograms. Two patients, one male and one female, were slightly obese and had confirmed

attacks of myocardial failure before their terminal illness and death from dissecting aneurysm.

In view of the serious nature of dissecting aneurysms of the aorta the favorable results achieved by surgeons is heartening. Blood vessel banks are becoming better equipped and adequately stocked with arterial homografts. The series of operations reported by DeBakey and Cooley[8], by Brown[14], and his associates at Bethesda, Maryland and by Julian[13] and his group in Chicago, attest to the widespread interest of surgeons in vascular operative procedures. Numerous other reports of ingenious operative procedures are extant. The important adjuncts of drug therapy to reduce blood pressure and aid hemostasis, and the employment of newer anesthetics have helped to reduce morbidity and mortality in surgery of the aorta. The technics for resection of aortic aneurysms are ever more in demand as people live longer and develop arteriosclerotic changes. The preference of arteriosclerosis for the abdominal aorta presages an increase in aneurysms both saccular and dissecting.

Summary

Ten cases of dissecting aortic aneurysm are presented. Nine were of the abdominal aorta and one of the thoracic aorta. The latter extended distally and induced abdominal symptoms.

The ten patients lived from 12 hours to 15 days after entering the hospital. Three patients had their condition correctly diagnosed clinically and in two of these brief x-ray studies disclosed the condition.

All patients had major symptoms referrable to the gastrointestinal tract and two were operated upon for supposed bowel obstruction. Dissecting aneurysm of the abdominal aorta deserves consideration in the differential diagnosis of gastrointestinal symptoms. In the reported cases there was sufficient time to secure the services of a vascular surgeon and attempt life-saving procedures.

Severe nutritional deficiencies were present in three of the ten patients who had died of dissecting aneurysms. In view of the association of such aneurysms with pregnancy, Marfan's syndrome and lathyrism, dietary habits and genetics assume considerable importance in evaluating such vascular lesions.

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INCREASED UROPEPSIN EXCRETION DURING TESTOSTERONE ADMINISTRATION*

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In a previous discussion and review of uropepsin[1], the various names given to this proteolytic substance, the methods of determination, and the physiopathologic knowledge of this enzyme were summarized. From the studies that have been made on uropepsin, it may be stated that the measurement of peptic activity in the urine gives an estimate of the basal state of gastric function over a given period of time[2]. If one is interested in determining the basal state of gastric function, it is easier and probably more accurate to perform daily assays of this urinary enzyme than to repeatedly measure basal acid secretion, the delayed return of acid secretion to normal after a stimulus, or basal motor activity.

Usually these three functions of the stomach are parallel. This is due to the fact that stress usually stimulates the activity of all gastric functions. Therefore, high values of gastric acid, uropepsin, and hypermotility are generally found in peptic ulcer and the opposite found in cancer of the stomach, old age, or prolonged atrophic changes of the gastric mucosa. This is not always true, however, because uropepsin and acid or motility levels of activity are not due to the same stimuli.

Gastric acids and motility respond to vagal and histamine (or gastrin) stimulation while uropepsin levels are determined more by adrenal cortical activity and are more constant. Unless normal adrenal cortical activity is present, no uropepsin or gastric acids will be present. In the presence of hyperactivity of the adrenal cortex, uropepsin measurements will be high but gastric acid response and motility may not be too excessive. When the uropepsin or adrenal cortical activity is normal or even low, excessive psychic or vagal stimulation may occur with high acidity and hypermotility.

Therefore, a laboratory procedure is now established which will give the state of stress or basal state of gastric function upon which the other functions of the stomach are only superimposed. It is this basal state of gastric function which, when evaluated more fully, may lead to unexpected answers regarding treatment.

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*Read before the Second Annual Convention of the American College of Gastroenterology, Chicago, Ill., 24, 25, 26 October 1955.

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Accepting the fact that adrenal cortical function primarily determines this basal state of function of the stomach, we are confronted with some confusing clinical observations. It is commonly accepted that women do not develop peptic ulcer to the same degree as men and the uropepsin level in women is slightly lower than in men[1]. Also, pregnancy usually brings relief of ulcer symptoms. These clinical observations have led to many investigations into the relationship of antiulcer substances being present in pregnancy and the effects of hormones on peptic ulcer[3].

Adequate studies have not been done in this field primarily because of the difficulty of obtaining repeated measurements of basal gastric function. Certainly there are many factors involved in the ulcer problem such as motility, diet, hormone secretions, nutrition, vascular changes, acidity, and others including the influence of direct or indirect ulcer inhibitory factors. Uropepsin studies

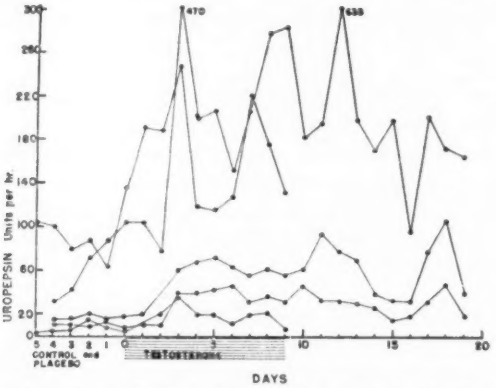

Fig. 1—Uropepsin values in medical students during control, placebo, and testosterone therapy periods. Placebo administration given before testosterone and in some instances after testosterone.

may clarify the significance of some of these factors when the uropepsin values are interpreted on the basis of a steady state or lack of unusual alarm or stress reactions.

The following study of the effect of testosterone on gastric function as measured by serial uropepsin determinations is similar to the studies made by Gray[4] using ACTH and cortisone and by us using Rauwolfia medication[5].

Methods

The technic of West et al[6] was used in the uropepsin determination*. This simpler method of assay depends on the rennin-like activity of activated

*We are grateful to Robert Liechti and Jack Kortzeborn for expertly doing the laboratory procedures.

pepsinogen and the length of time it takes this enzyme to cause coagulation of milk proteins.

It was desirable to use: 1. male subjects who had no evidence of disease of the stomach, 2. to give large controlled dosage of the testosterone, 3. to eliminate as much as possible any alarm reaction incurred in the administration of the drug and 4. to use the double blindfold technic with a placebo.

Two groups of subjects were chosen for study. A group of medical students undergoing a prolonged nitrogen and fluid balance study on an ambulatory basis were given placebo injections of sesame oil during one period of study

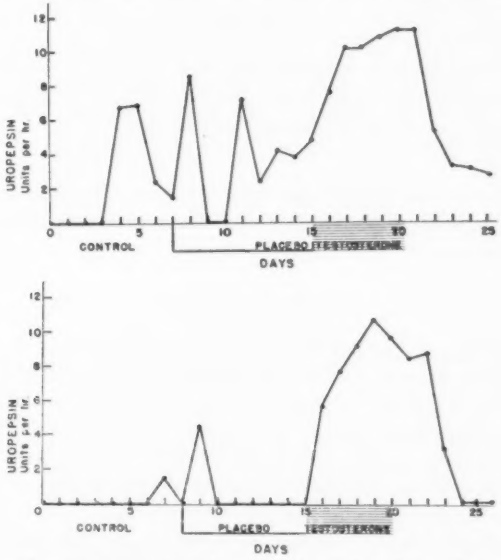

Fig. 2—Two curves showing uropepsin values in older male subjects during control, placebo, and testosterone therapy periods.

and testosterone propionate 100 mg. in oil during another period of study with control periods before, between and after each period. During the second course of this study†, when the subjects were accustomed to injections, aliquots of 24-hour urine collections were assayed for uropepsin.

Another group of male subjects who were in the Los Angeles County Hospital in the age group of 50-60 years were also studied during a control period, a placebo period of injections with sesame oil and during the period

†We are grateful to Dr. E. Raymond Borun, now Assistant Research Cardiologist, University of California at Los Angeles Medical Center, for permitting us to have aliquots of urine and the results of his work will be presented elsewhere.

of the daily injection of 100 mg. of testosterone propionate in oil. These patients were hospitalized for chronic injuries but were on an ambulatory basis and had no gastrointestinal symptoms.

A limitation of the uropepsin determination became evident in studying many of these older, indigent patients. Frequently, with the limited activity of ambulatory hospital conditions and especially seen when the patients were put at bed rest, the pH of the urine would rise to 8.5-9.0. At this pH pepsinogen is slowly and irreversibly deactivated[6] and the assay showed a fall toward zero at these times.

Results

In the group of medical students, Figure 1 shows the rise in every instance from control and placebo periods to often double the amount of uropepsin during the testosterone period of administration. A slow decline to control levels then occurred.

Figure 2 shows two typical examples of more significant elevation in the older indigent subjects with possibly the effect of some alarm reaction with the placebo injections.

Comments

In both groups, a rise in uropepsin excretion occurred and this would suggest that testosterone in addition to adrenal cortical function played a part in the basal state of gastric function. The effect was greater in the older group where glandular secretions would be expected to be lower. Poor nutrition in this group, as has been previously reviewed[1], is no doubt partly responsible for the low uropepsin levels. Normal variations in pH of the urine have shown no influence on uropepsin excretion[1] but highly alkaline urine will destroy this enzyme and gastric function cannot be assayed by this method under such conditions.

Previous studies in uropepsin excretion during cortisone and testosterone therapy in patients with systemic disease has been discussed[1] and in these patients the uropepsin levels usually do not rise.

This has been explained on the basis of the systemic disease reducing the capacity of the gastric mucosa to respond normally to cortisone or testosterone therapy or that the diseased tissue takes up these hormones preferentially so that there is no excess of the drug to overstimulate normal tissue.

Conclusions

The daily administration of testosterone to normal male subjects is followed by a significant increase in the basal state of gastric function as measured by

uropepsin determinations. This is similar to but not so great as the uropepsin rise with ACTH or cortisone. These and other studies indicate the usefulness of serial uropepsin determinations to measure the effect of medication on the basal state of gastric function.

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THE INFLUENCE OF SEX AND AGE ON UROPEPSIN EXCRETION*

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The presence in the urine of a proteolytic enzyme has been known since 1861[1], and an extensive review of this subject to 1947 was made by Bucher[2]. A considerable amount of work, however, has appeared in the literature since that time. Because of the pepsin-like character of the enzyme, it was originally called uropepsin. Later evidence[3-6] demonstrated that the enzyme is "endocrine" pepsinogen, being secreted by the gastric glands directly into the blood stream. Because the term "uropepsin" has been used widely in the literature and, for the sake of brevity, it will be used here in preference to "uropepsinogen", though the latter is the correct name.

A functioning gastric mucosa appears to be necessary for its presence, for little or no uropepsin was evidenced in pernicious anemia[3,7-15] and after total gastrectomy[6,8-11,13,14,16-18], though two reports[18,19] of activity following gastrectomy have appeared. Low values were found in atrophic gastritis[8,20]. Although normal values have been reported in subjects with anemias other than pernicious anemia[11,12], evidence[11,14] has indicated that patients with an iron deficiency anemia with true achlorhydria, may show a level of uropepsin as low as that demonstrated in pernicious anemia.

A correlation has been shown to exist between pepsin secretion into the stomach and uropepsin excretion[11,21-25] but, under certain conditions, such a correlation was not found[24,26]. A definite rise in uropepsin output has been noted after the injection of insulin[27-29], but the effect of histamine on the excretion of this enzyme is not clear. After administration of histamine in man, both no significant change in uropepsin output[7,30] and a clear increase[29] have been reported. Caffeine-histamine treatment in cats[31] produced variable results depending on experimental conditions. Kowalewski[30] injected large doses of histamine into guinea pigs protected by an antihistaminic drug. A marked increase in plasma pepsinogen was demonstrated as well as a rise, though to a lesser degree, in uropepsin. Smoking[25,31a,31b] brings about a somewhat increased

*From the Department of Gastrointestinal Research, Medical Research Institute of Michael Reese Hospital, Chicago, Ill. Supported by the American Cancer Society, Illinois Division. The Department is in part supported by the Michael Reese Research Foundation.

For their cooperation on this project, we wish to express our appreciation to the School of Nursing and the House Staff of Michael Reese Hospital; the personnel of Nelson Morris Research Institute; and the Director and personnel of Drexel Home for the Aged.

excretion of this enzyme. Concerning a relationship between gastric acidity and uropepsin, a lack of correlation between these two factors has been noted[7,15,32].

Understandably, the relation of uropepsin excretion to gastrointestinal disease has attracted considerable attention. In some cases of gastric cancer, uropepsin may be absent from the urine[8,33], but, mainly, normal[9,10,13,19] or low[14,15,19,20] values are found. On the other hand, peptic ulcer is reported to cause an increased excretion of this enzyme[7,22]. Dividing the ulcer cases with respect to site, patients with gastric ulcer have yielded, with some exceptions[15], normal values[9,10,13,14,19,20], while those with duodenal ulcer have shown a tendency toward a high excretion rate[9,10,13-15,19,20,34]. Several workers have examined this problem in even greater detail. A report by Hirschowitz[35], who made an extensive analysis of the relation of uropepsin values to peptic ulcer with regard to site and duration of the ulcer and the sex of the patient, demonstrated normal values for female ulcer patients irrespective of the site of the lesion and length of history. Conversely, in males, these factors played a part, for when the gastric ulcer was on the lesser curvature, the uropepsin was normal but, when it was at or beyond this site (antral), high excretion values were obtained. Likewise, in males with duodenal ulcer and a history of less than five years, the values were normal, but were high with a history of over five years. Some of these findings are confirmed by Balfour[36]. On the other hand, Eastcott[19] did find increased uropepsin values for women with duodenal ulcer, though they were lower than those for men, and Sircus[14] could not confirm that the length of history in duodenal ulcer or the site of the gastric ulcer had any relation to the uropepsin excretion. He did find a significant difference between the mean rate of excretion in active duodenal ulcer and cases in remission. Also, a sex difference was apparent for, although the values were high in both men and women in the active phase, in remission the values of the male group decreased somewhat but still remained high, while those for the female group returned to normal. Gray et al[15], however, noted that "the complications of peptic ulcer do not appear to alter uropepsin excretion".

Originally, it was thought that the uropepsin test might be a useful aid in the diagnosis of duodenal ulcer and some investigators do feel it has a place toward this end[14,15,19,37], while others, because of the large amount of overlapping found between values in normal subjects and those in patients with duodenal ulcer, have concluded that it is of little value[10,12,34,35]. It is of interest to note that, in a comprehensive study concerning the relationship of the concentration of pepsin in the gastric juice to gastric and duodenal disease, Vanzant et al[38] reluctantly concluded that "the individual variability in pepsin readings is so large and the overlapping of distribution so great that estimations of this ferment can seldom have much diagnostic value". Another line of investigation which has been recommended[10-12] is the use of this test for the study of gastric secretion in anemias and the diagnosis of pernicious anemia.

Gray and his colleagues[8,15,22,33,39-42] have aroused considerable interest concerning the interrelationship of physical and emotional stress and the pituitary and adrenal glands to gastric secretion. They found that the administration of ACTH to normal persons over a period of time produced a definite increase in the free acid and pepsin secretion of the stomach and in uropepsin excretion. It was further demonstrated that this effect is mediated through the adrenal cortex and that a functioning gastric mucosa is necessary for the response. Other workers have corroborated the uropepsin rise after ACTH administration[19,24,29,43-45] and, in addition, have reported on the increase in uropepsin excretion brought about by different forms of "stress", such as adrenalin, bacterial substances, fever, "situations of stress", etc.[44,46-50]. This phenomenon would offer an explanation for the high pepsin secretion reported to be found in tense, nervous individuals (pseudo-ulcer)[38,51] and for "high normal" uropepsin values, thus accounting for the overlapping of results between a normal and a duodenal ulcer group. Also, it might account for the fact that among male prisoners, all of whom would be under considerable emotional tension, no higher average uropepsin value was demonstrated for a group with duodenal ulcer than for those without the symptoms of this disease[52].

Other relationships between adrenal activity and gastric secretion[53-55] and also the excretion of this enzyme[56,57] have been noted. In addition, the uropepsin response to "stress" stimulation (either hormonal or other) has been found to parallel an increase in the urinary corticosteroids[15,58] and a decrease in eosinophiles[28,43], all of which has led to the recommendation that the uropepsin test be used, along with other methods, as a measure of the activity of the adrenal cortex[43,46,47]. Some investigators, however, have not obtained consistent results along this line of research and so feel that the clinical usefulness of uropepsin determinations as a measure of adrenal activity is slight[24,44].

Several normal factors, namely sex and age, have been reported to have a bearing on gastric secretion. Men are known to secrete more free acid than women, and a steady increase in the incidence of achlorhydria with age has been noticed[59]. Likewise, the concentration of pepsin in gastric juice is higher in males than females and its secretion decreases with age[60]. Consequently, the question arises as to whether sex and age have an effect on uropepsin. Such knowledge would be necessary for the proper evaluation of uropepsin data. In view of contradictory results in the literature, we undertook a study of this problem in a statistically adequate number of subjects.

Method

Uropepsin excretion values were determined on 282 normal individuals, 113 males and 169 females, who had no known symptoms of gastrointestinal

or other disease, and no elevated body temperature or leucocytosis. With a few exceptions, these subjects may be grouped as follows: 1. those 13 years and under were admitted to the hospital for tonsillectomy; 2. those 17-60 years were hospital personnel; 3. those over 60 years were living in a home for the aged. The people in the latter group were in average good health except for the usual physiological changes found in aging; none was on a specific therapy; all were without acute cardiac symptoms and endocrine disturbances including diabetes.

Twelve-hour urine specimens, collected under toluene from 8:00 P.M.-8:00 A.M., were used, and each subject was instructed to eat or drink nothing

TABLE I

DISTRIBUTION OF UROPEPSIN EXCRETION RATES (UNITS PER HOUR)

Age Years	Number of Individuals	Range of Uropepsin Rates	Mean* Uropepsin Rate	Percentage Distribution of Uropepsin Rates				
				0-50 Units/Hr.	51-100 Units/Hr.	101-150 Units/Hr.	151-200 Units/Hr.	Over 201 Units/Hr.
Males								
3-13	9	7-130	64 ± 13	33	44	22		
19-25	18	35-261	144 ± 14	6	28	22	22	22
26-60	52	25-645	176 ± 16	6	29	19	19	27
61-91	34	8-300	120 ± 12	21	21	26	15	18
Females								
3-9	8	8-130	44 ± 13	75	12	12		
17-25	53	14-228	73 ± 6	45	32	17	4	2
26-60	54	24-300	108 ± 10	24	31	20	15	9
61-100	54	6-316	98 ± 9	33	24	20	17	6

*Mean ± standard error of the mean

but water during that period. The determinations, with few exceptions, were performed on the same day that the collection was completed. When this procedure could not be followed, the samples were refrigerated immediately and at no time were they kept more than one week. Uropepsin was determined by a modification of the Anson and Mirsky hemoglobin method for pepsin[61], described elsewhere, following the method for nondialyzed urine[62]. A unit of uropepsin is defined as that amount of enzyme which releases 1 mEq. x 10^{-4} of tyrosine or "tyrosine-like" substances from the hemoglobin substrate in a 10 minute incubation period at 37° C.[9]. Uropepsin values are reported as units excreted per hour.

In addition to the normal group, a number of uropepsin determinations were carried out on men and women in the "over 60" age group who had arthritis treated with cortisone, diabetes, or inactive peptic ulcer.

Results

The distributions of uropepsin excretion rate for males and females are shown for various age groups in Table I*. Because of the marked skewness of

TABLE II

Logarithms of Uropepsin Excretion Rates: Means, Variances and Analysis of Variance*

Males			Females		
Age Years	Logarithms		Age Years	Logarithms	
	Means	Variance		Means	Variance
3-13	1.692	0.1528	3-9	1.516	0.1300
19-25	2.092	0.0561	17-25	1.757	0.0811
26-60	2.142	0.0922	26-60	1.945	0.0862
61-91	1.950	0.1569	61-100	1.818	0.1062

Analysis of Variance*

Source Of Variation	Degrees Of Freedom	Mean Square	F
Sex	1	2.712	22.0†
Age	3	1.113	9.2†
Sex-Age Interaction	3	0.111	<1.0
Individuals	274	0.1226	

*Using procedures appropriate for disproportionate subclass numbers. (Snedecor, G. W., Statistical Methods, 4th Ed., 1953, p. 284. See also Biometrics, **9**:253, 1953)

†P <1%

the distributions and correlation between the means and standard deviations, sex and age differences could not be tested by applying t-tests or analysis of variance to the data as such. The logarithms of the excretion rates, however, are normally distributed and there is no association between mean and variance. Statistical treatment of the logarithms, including the analysis of variance, is

*Statistical analysis of the results was performed by Dr. H. Silverstone.

given in Table II. These tabulations indicate that the average uropepsin excretion rate is significantly greater (by 60 per cent on the average) in males than in females, and this sex differential is not noticeably dependent on age. Also, the uropepsin excretion is significantly lower in pre-adolescents than in adults. An apparently significant decrease appears in the "over 60" male subjects with a corresponding suggestion of a decrease in the female group.

The data on uropepsin excretion in disease are summarized in Table III. On the average it is higher (of questionable statistical significance) among diabetics and patients with inactive peptic ulcer than in "normal" individuals of the same age class. Female patients with arthritis treated with cortisone, 50-100 mg. per day, did not show increased uropepsin values.

Comment

The literature reveals conflicting conclusions concerning the effect of sex and age on uropepsin excretion in normal individuals. On the one hand, no difference between the sexes[14,15,35] and no effect of age[14,19,35] on uropepsin values were demonstrated. Investigating plasma pepsinogen levels in a large group, Mirsky[63] found no significant difference in values between the sexes of each age group, except for the 70-79 year group in which the average value of the male group significantly exceeded that of the female group. He did find, however, an effect of age, the pepsinogen activity of the plasma "increasing with age until the third decade and remaining fairly constant thereafter". This same trend is indicated by our data for uropepsin excretion, except that a decrease is suggested in the "over 60" age group.

Several investigators[19,47] have reported higher uropepsin values for men than for women in conformity with the findings presented here. These results correlate with higher gastric pepsin[60] and free hydrochloric acid[59] secretion in men as contrasted with that of women. The secretion of pepsin[60] and free acid[59] has been shown to decrease with age. Balfour[36] observed a drop in uropepsin excretion in the older age group, as did Gray et al[15] in persons 70-83 years. In this study, a tendency toward decreased rates in the subjects over 60, particularly in men, is noted.

It can be seen that normal values for both men and women in all age groups, as well as those in the groups with disease, vary over a wide range, an observation noted by others. While nominal differences in values, when determinations were repeated on the same person from day to day[15,64] have been found generally, variations of several hundred per cent have been reported[26]. Too, there is the inherent difficulty of assembling a "normal" group. The average investigator must rely on the word of the subject as to the state of his health, but there are people in the population who harbor an ulcer unknown to them until obvious symptoms appear. As was noted in the introduction, "stress" can increase uropepsin excretion. Who can tell to what fears, anxieties

and apprehensions any "normal" individual may be subject? Even he himself may be only vaguely aware of them. Finally, a syndrome called "pseudo-ulcer" has been described[38] in which gastric pepsin secretion is elevated in men but is normal in women. All such individuals could be found in any "normal" group. These observations emphasize the fact that here we are dealing with a problem influenced by a number of uncertain factors and subject to wide physiological variations. Hence, it is not to be wondered at that in a disease state such as peptic ulcer, influenced as it is by nervous factors, workers have differed in their results and conclusions. One may well ask concerning the value of uropepsin determinations. From a diagnostic point of view, the test is inconclusive and at best holds some significance only if the result is

TABLE III

UROPEPSIN EXCRETION RATES IN THE AGED (OVER 60 YEARS) IN DISEASE

Disease	Sex	Number Of Individuals	Uropepsin Excretion Rates: Units/Hr.		Normal Values (From Table I)
			Range	Mean*	
Diabetes	Male	8	49-425	192±47	120±12
Diabetes	Female	8	38-317	142±35	98± 9
Inactive Peptic Ulcer	Male	6	33-536	236±75	120±12
Arthritis (Cortisone Treated)	Female	6	13-129	84±21	98± 9

*Mean ± standard error of the mean

high or low, an intermediate finding being of no aid. As a research tool, in studying pernicious anemia and other types of anemias, in gastrointestinal studies and in studies on adrenal secretion, the uropepsin assay holds considerable interest at the present time.

SUMMARY AND CONCLUSIONS

1. Uropepsin excretion rates were determined on 282 "normal" subjects, 113 males and 169 females, with an age range of 3 to 100 years.

2. The average uropepsin excretion rate is significanly greater (by an average of 60 per cent) in males than in females.

3. Pre-adolescents have a significantly lower uropepsin excretion rate than adults. The data suggests a tendency toward a decreased excretion rate in the "over 60" age group, this tendency being more marked in men than in women.

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BENIGN DUODENAL TUMORS

Three Case Reports

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Duodenal tumors are seldom considered in the differential diagnosis of gastrointestinal bleeding. While the incidence of these tumors is small, the correct management depends upon an accurate diagnosis. Many tumors of the duodenum are entirely asymptomatic. These have been present at post-mortem examinations as incidental findings and were not related to the cause of death. The tumors, however, may not be silent and may mimic duodenal ulcers. If these tumors attain sufficient size, they may cause obstruction. Gastrointestinal bleeding, notably melena, may be the only complaint. Pain may be present in the right upper quadrant and may lead one to suspect gallbladder pathology.

TABLE I

Patients Hospitalized for Gastrointestinal Bleeding from Benign Causes
January 1953–May 1955

Cause	Number	Per Cent
Duodenal ulcer	45	66
Hiatus hernia	14	20
Esophageal varices	4	6
Tumors of duodenum	2	3
Cause unknown	2	3
Gastric ulcer	1	2
Total	68	100

From January, 1953 to June, 1955, 68 patients of the Jamaica Medical Group were admitted to the Horace Harding Hospital, Elmhurst, N. Y., because of massive gastrointestinal bleeding. An analysis of these cases is seen in Table I. Duodenal tumors represent about 3 per cent of all cases admitted for gastrointestinal bleeding from benign causes.

Case Reports

Case 1:—A 53-year old white male was admitted, on 7/6/51, to the Horace Harding Hospital. The patient had a past history of peptic ulcer which was

*From the Jamaica Medical Group, Jamaica, N.Y.

made seven years ago, at which time he had melena. During the past seven years, he was treated with a variety of ulcer-type of medications and diet with partial control of the symptoms. A gastrointestinal series performed in 1949 was negative. The patient, however, still complained of bloating and dyspepsia associated with dietary indiscretion. For several months, prior to admission to the hospital, the patient had been complaining of increasingly severe epigastric pain. On the morning of admission to the hospital, he had two large tarry stools which were then followed by a frank hematemesis. On admission to the hospital, his red blood cell count was 3,800,000, hemoglobin 11.8 gm., white blood count 17,100, polymorphonuclear leucocytes 76 per cent, lymphocytes 20 per cent and monocytes 4 per cent. The patient was given blood transfusions and intravenous feedings. He was then placed on a Meulengracht diet, antispasmodics and antacids. The gastrointestinal hemorrhage spontaneously arrested

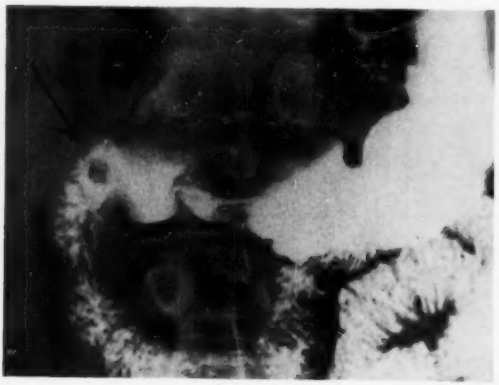

Fig. 1—Roentgenogram of stomach and duodenum of the patient in Case 1, showing a rounded defect just beyond the duodenal bulb. Exploration revealed a lipoma.

itself and he was discharged to his home, on 7/15/51 on an ulcer regimen. A gastrointestinal series was performed one month later. This revealed that the esophagus and stomach were normal. The duodenal bulb appeared normal but, just beyond the bulb, there was a 1 cm. rounded radiolucent filling defect, indicative of a polyp in the duodenum (Fig. 1). Although this was not visualized on all the films it was nevertheless felt to be a fairly definite finding, as it was quite striking on the two films on which it was seen. It was also suggestive on some of the other films, but was probably covered up in part with barium. A review of the gastrointestinal series of 1949 showed the same shadow in the same area on one of these films.

Because of the gastrointestinal series findings, the patient was re-admitted to the hospital on 9/6/51. At this time, he was entirely asymptomatic. His red blood cell count was 5.25 million, hemoglobin 12.5 gm., white blood cell count

9,900, 52 per cent polymorphonuclear leucocytes, 43 per cent lymphocytes, 3 per cent eosinophiles and 2 per cent monocytes. At operation, a polyp was removed from the second portion of the duodenum by duodenotomy. The patient was discharged from the hospital on 9/22/51 and was entirely asymptomatic. The follow-up four years later, revealed that he was still asymptomatic.

Pathological Report:—The specimen is a round polypoid mass 1 cm. in diameter. Microscopic examination reveals the presence of glandular elements, representing Brunner's glands, arranged in an orderly fashion. There is an overlying tumor mass of adipose tissue which is well demarcated. The tumor consists of polygamal adipose tissue cells divided into lobules by thin connective tissue septa.

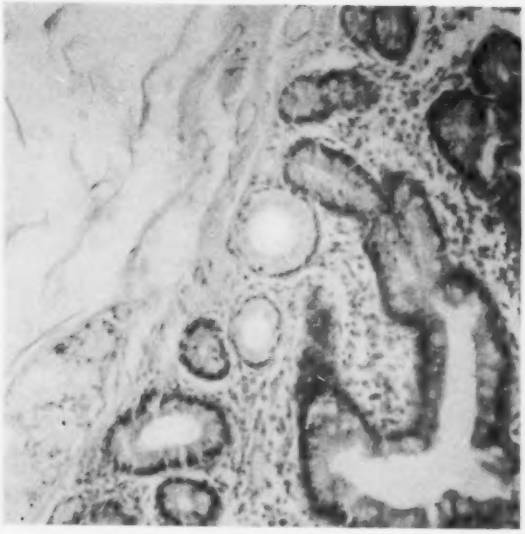

Fig. 2—Photomicrograph of duodenal lipoma removed at operation on the patient in Case 1. (x160).

Diagnosis:—Submucosal lipoma of duodenum.

Comment:—A lipoma of the duodenum caused peptic ulcer symptoms for seven years. There was one episode of severe gastrointestinal bleeding. A duodenal tumor was diagnosed roentgenographically preoperatively. The lipoma was excised with complete amelioration of symptoms.

Case 2:—A 33-year old housewife, was admitted to the Horace Harding Hospital on 12/8/54. She had complained of slight epigastric pain and nausea for three days prior to admission. She had no gastrointestinal symptoms prior to this. The patient vomited some clear, yellow fluid on one occasion and

complained of weakness. The following day, she had two black bowel movements and became very weak and dizzy. For the next 24 hours, she became progressively weak and pale and required hospitalization.

On admission, the patient was in no distress but markedly pale and weak. Otherwise, the physical examination was within normal limits. The abdomen was soft; there was no tenderness; the liver and spleen were not palpable; there were no palpable abdominal masses. The red blood cell count was 1,710,000; hemoglobin, 4.8 gm.; white blood cell count was 12,600 with 80 per cent polymorphonuclear leucocytes and 20 per cent lymphocytes. The hemato-

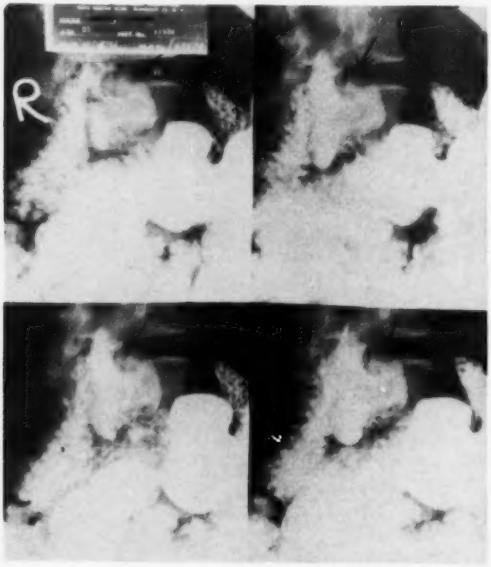

Fig. 3—Spot roentgenograms of duodenal bulb of the patient in Case 2, showing an indentation of the lesser curvature. Exploration revealed a pedunculated leiomyoma.

crit was 16 per cent. The stools were black and strongly positive for blood by the benizidine test.

The patient received 4,000 c.c. of whole blood by transfusion. On the fifth day, the tarry stools stopped. A gastrointestinal series was performed revealing an indentation of the lesser curvature of the duodenal bulb which was thought to represent an ulcer deformity or extrinsic pressure (Fig. 3). The gallbladder series was negative. The patient was operated upon on December 20, 1954. A portion of the wall of the second portion of the duodenum was removed. This included a pedunculated tumor which was about one centimeter

in diameter. A posterior gastroenterostomy was performed. Her postoperative course was uneventful. Four months later she was seen and was asymptomatic.

Pathological Report:—An irregular polypoid mass, one centimeter in diameter composed of soft slight friable tannish grey tissue was seen. Histological description revealed a cellular growth situated in and merging with the muscular layer of the duodenum (Fig. 4). The tumor elevated the duodenal mucosa over it, however, the mucosa appeared intact. The tumor was composed of elongated fusiform cells resembling smooth muscle cells, and nearly always orientated and arranged in interwoven bundles forming a well organized pattern. There were, however, some fields which showed cellular pleomorphism and slight loss of organized structure.

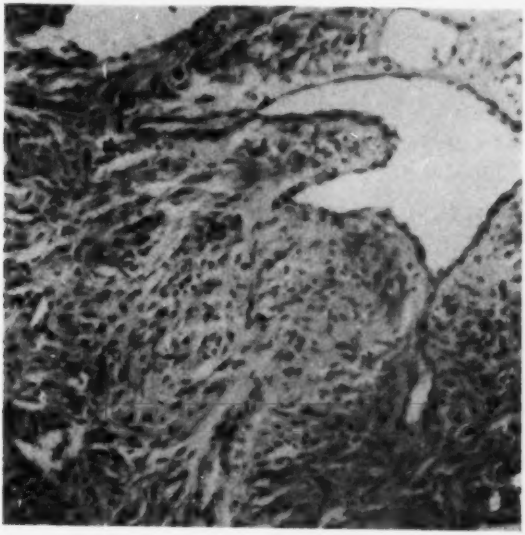

Fig. 4—Photomicrograph of leiomyoma removed at operation on the patient in case 2. (x160).

Diagnosis:—An actively growing, cellular leiomyoma.

Comment:—A severe gastrointestinal hemorrhage was caused by a leiomyoma of the duodenum. The patient was asymptomatic before the episode of bleeding. Roentgenographic study revealed a deformity of the duodenal bulb. Since the removal of the tumor, there has been no further gastrointestinal bleeding.

Case 3:—A 42-year old white male was seen in February, 1955 for peptic ulcer symptoms. He had a past history of peptic ulcer for 25 years and had increasingly severe recurrences of dyspepsia, epigastric pain, cramps and

heartburn. Four months prior to hospitalization, the patient had only slight relief of his symptoms from antacids, sedatives and antispasmodics. One month prior to admission, he noted loss of appetite and occasional vomiting. Melena was also noted on occasion. The patient had a gastrointestinal series which revealed a normal esophagus and stomach. The duodenal bulb, however, was greatly deformed and moderately irritable. There was considerable dilatation and delay in the duodenal loop. Two hours' progress of the barium meal was normal. Conclusions from the gastrointestinal series was that he had a duodenal ulcer with "duodenal ileus". (Dilatation and delay in the duodenal loop.) The patient was again treated with an ulcer diet and antacids and medication with poor response. In March, 1955 he had a massive gastrointestinal hemorrhage and required emergency hospitalization. At this time, his red blood cell count was 2.6 million, hemoglobin 8 gm., white blood cell count 8,700, polymorphonuclear leucocytes 71 per cent, lymphocytes 23 per cent and monocytes 3 per cent. The hematocrit was 22 per cent. The patient was given blood transfusions, antacids and sedatives. Three days later the bleeding subsided spontaneously. A subtotal gastrectomy was performed and an active peptic ulcer was found in the first portion of the duodenum. As an incidental finding on transecting the duodenum, a 1 cm. sessile tumor was noted in the second portion of the duodenum beyond the ulcer site. This tumor was resected.

Pathological Report:—The specimen consists of a slightly elongated polyp with a bulbous tip 3 cm. in length with a rather narrow base. It is covered by grossly intact mucosa. The polyp is composed of loose submucosal areolar tissue covered by normal appearing duodenal mucosa. Near the tip, there is a large irregular mass of well differentiated pancreatic tissue situated predominently in the submucosa. The *muscularis mucosae* is intact over the surface of the mass except for a defective area in the center where this layer is missing and the pancreatic tissue extends into the mucosa itself. The mucosa becomes markedly attenuated at this site. There is no evidence, however, of ulceration or inflammation. The pancreatic tissue consists of closely packed glandular acini resembling those of normal pancreas. The epithelial cells are pyramidal in shape and have a dark homogenous basal portion and a paler supranuclear portion containing eosinophilic refractile secretory granules, suggesting that the glandular tissue is actively functioning. No islet tissue is noted. There are several included pancreatic ducts, some toward the base of the polyp showing slight dilatation and having well differentiated muscular walls. The fibrillar stromal tissue near the base of the polyp is oriented longitudinally in the axis of the polyp, suggesting that the polyp was subjected to traction, such as from peristalsis. There is no evidence of malignancy.

Diagnosis:—This is a duodenal polyp due to aberrant pancreatic tissue probably congenital in origin and representing aberrant differentiation of intestinal mucosa during its formative states.

Comment:—A duodenal polyp composed of aberrant pancreatic tissue was discovered as an incidental finding in a patient who had a subtotal gastrectomy for a bleeding duodenal ulcer.

Comment

Raiford[1] found that small intestinal tumors comprise about 9 per cent of all tumors of the gastrointestinal tract in 56,500 autopsies. Benign small bowel tumors made up 24 per cent of all gastrointestinal tract tumors. Adenomas are the most commonly found and aberrant pancreatic tissue next in frequency. The latter are seldom symptomatic. Leiomyoma have a tendency to bleed and rarely show malignant changes. Lipomas may attain large size and cause symptoms. They are frequently pedunculated. Malignant small bowel tumors comprise 5 per cent of all gastrointestinal tract tumors. Carcinomas are more frequently found in the duodenum than any other portion of the small bowel. Sarcomas and lymphomas are rare. Hoffman and Grayzel[2] in their review of 64,300 surgical specimens and 4,480 autopsies found 14 benign duodenal tumors. All were asymptomatic and discovered accidentally. Ebert et al[3] in an analysis of 25,000 autopsies from the Boston City Hospital found 23 primary duodenal tumors. Eight of these were benign and 12 were malignant. Five of the benign tumors were incidental findings. Only one, a lipoma, had gastrointestinal bleeding. Joergenson et al[4] reported 56 tumors of the duodenum; 17 were benign and 39 malignant. Fifteen of the benign tumors were accidental autopsy findings. The 2 cases having symptoms complained of chronic, progressive obstruction and gastrointestinal bleeding. The cases of carcinoma had nonspecific symptoms which were referred to the stomach. These symptoms included anorexia, gaseous erructation, vomiting, right upper quadrant pain, weight loss and gastrointestinal bleeding. Twenty-five per cent of these cases had jaundice.

Several others have reported on small series of symptomatic benign duodenal tumors. Campbell's[5] two cases of leiomyoma had gastrointestinal bleeding; one was treated originally as a peptic ulcer. The second revealed a filling defect on x-ray examination. Straus[6] reported one case of leiomyoma of the duodenum. This patient was originally thought to have gallbladder disease. There was an associated secondary anemia due to gastrointestinal bleeding. X-ray examination revealed a filling defect of the duodenum. The one proved case of Woodward[7], was an adenomatous polyp. The only symptom was nausea.

Other less common types of benign lesions, that have been found in the duodenum, include lymphangiona, hemangioma, gastric rests, neurofibroma and argentiffine tumors. Two cases of carcinoid of the duodenum have recently been reported. One case[8] had gastrointestinal bleeding; the second case[9] cyclic vomiting.

The diagnosis of tumors of the duodenum can be suspected from positive roentgenographic study of this area. A gastrointestinal series may not be diag-

nostic and actual confirmation of course can only be obtained at operation. The roentgenogram may fail to show the tumor if the flow of barium through the duodenum is rapid. A large lesion may impede the flow of barium. The tumor may cause a deformity of the bulb or cause a filling defect. Some tumors, especially the lipomas, may be pedunculated and project into the lumen, others may be sessile. They may extend from the subserosal region as well as into the lumen.

Asymptomatic duodenal tumors are seldom discovered during the lifetime of the patient and thus represent no problem of treatment. If the lesion is symptomatic and is suspected from roentgenographic studies, surgical removal is the preferred treatment.

Summary

Tumors of the duodenum are usually asymptomatic. They may, however, cause gastrointestinal symptoms which may mimic peptic ulcer or gallbladder disease.

Three cases of benign tumors of the duodenum are presented.

Some comments as to the incidence, and symptomatology of these are offered.

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SPLENIC VENOGRAPHY IN PORTAL CIRRHOSIS OF THE LIVER

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Splenic venography by the percutaneous route was first carried out by Abeatici and Campi[1] in dogs and by Leger[2] in man. Soon afterwards, Boulvin and co-workers[3] carried out the same procedure in a patient suffering from cirrhosis of the liver and in another who had extrinsic obstruction of the splenic vein. They suggested that the procedure might be useful for the differentiation of intrahepatic and extrahepatic block. Dreyer and Budtz-Olsen[4] used the method in 11 patients and pointed out its value in determining the site of the obstruction in patients with portal hypertension.

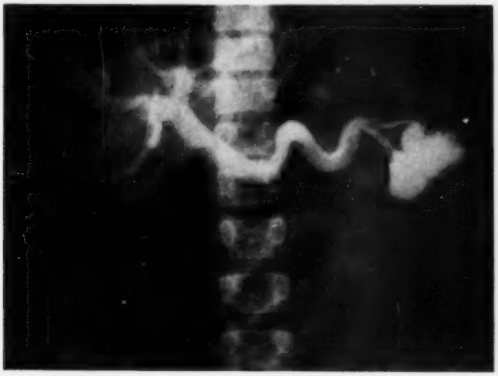

Fig. 1—Normal splenic venogram. Splenic vein and portal vein with its intrahepatic branches are clearly seen even as far as the periphery of the liver.

Konar[5] demonstrated a splenic venogram of a patient with portal hypertension. The inferior mesenteric vein was prominently visualized. Konar and Sen Gupta[6] described their experiences of splenic venography in 23 patients. They suggested that the method might be used in determining the size and patency of the splenic vein, in differentiating intrahepatic from extrahepatic block of the portal vein, and in assessing the degree of portal hypertension. They later[7] pointed out that the procedure might be useful in demonstrating esophageal varices in patients with portal hypertension. Fuld and Irwin[8] described their experiences with splenic venography in more than 50 patients.

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Present Investigation

Twenty-seven patients with portal cirrhosis of the liver were studied. The disease was diagnosed on clinical grounds. Biochemical investigations and observation of the patients in the hospital helped in establishing the diagnosis.

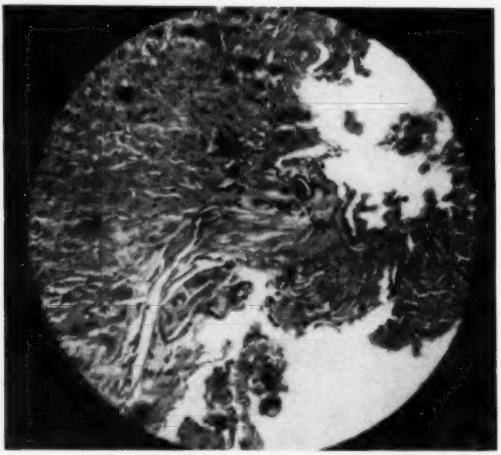

Fig. 2—Case 1 (Early case). Proliferation of bile ducts and early fibrosis. (Hematoxylin and eosin. x350) Tissue removed by needle biopsy.

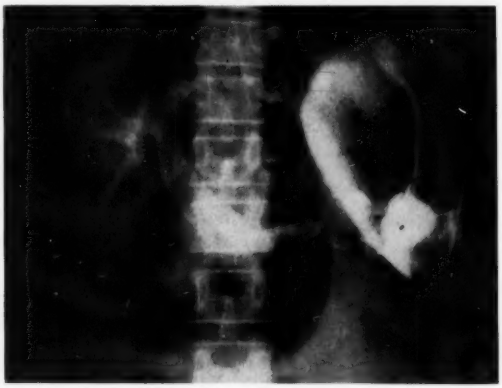

Fig. 3—Splenic venogram of Case 1 (Early case). The intrahepatic branches are thinner than normal and are not visible as far as the periphery of the liver. The splenic and extrahepatic portion of the portal vein are slightly dilated and the gastric veins are faintly visible.

In some patients, needle biopsy of the liver was done and in patients on whom surgery was performed, a piece of liver tissue was removed for pathological examination. The patients were divided into three groups—early, moderately

TABLE I

EARLY CASES

Case No.	Name	Age	Sex	Hematemesis and/or melena	Veins in anterior abdominal wall	Ascites		Cachexia	Liver	Spleen	Blood				Date of Splenic Venography	Date of discharge from hospital or of death	Remarks
						Duration	Amount				T.P. gm.%	Alb. gm.%	Glob. gm.%	Bilirubin mg.%			
1	S.L.P.	36	F	–	–	2M	+	+	2F, firm	3F	6.2	2.6	3.6	0.1	11/24/54	Still in hospital	Marked improvement. No ascites.
2	P.C.P.	42	M	+	+	–	–	–	N.P.	5F	6.1	2.7	3.4	0.4	8/13/54	9/10/54	Died due to splenectomy.
3	N.C.B.	12	M	+	++	–	–	–	3F, hard	3F	7.4	3.1	4.3	0.2	5/ 2 /52	11/ 3 /52	Improved after splenectomy. Still keeping well.
4	K.C.M.	28	M	–	–	–	–	–	2F, firm	5F	6.4	2.6	3.8	0.2	1/ 7 /54	3/ 7 /54	Early cirrhosis in a case of tropical splenomegaly.
5	N.B.B.	40	F	–	–	–	–	–	3F, hard	5F	6.1	2.7	3.4	0.1	3/25/54	4/16/54	
6	S.C.M.	40	M	–	+	1M	+	+	N.P.	3F	5.4	2.6	2.8	0.1	2/10/54	4/16/54	Improved, no ascites. Again admitted with ascites on 1/4/55. Improving.
7	B.K.M.	35	M	–	–	–	–	–	N.P.	1F	6.1	3.7	2.4	0.4	12/26/54	1/ 7 /55	Cirrhosis detected during operation for peptic ulcer.

– Absent
\+ Slight
++ Moderate
+++ Marked
M Month
Y Year
F Fingers below costal arch
N.P. Not palpable
T.P. Total protein

advanced, and advanced–clinical classifications based on the overall evidence of severity of the disease. Patients in the "early" classification of portal cirrhosis of the liver had slight or no ascites and their general condition was fair. Those classed as "moderately advanced" had moderate ascites and some cachexia, while those in the "advanced" classification had marked ascites and moderate cachexia. Clinical features and biochemical findings have been summarized in Tables I, II and III.

Method of Splenic Venography

The method of Konar and Sen Gupta[6] was followed with minor modifications. Bleeding and clotting time was determined because unusual prolongation would be a contraindication for this procedure. Ten mg. of Vitamin K was

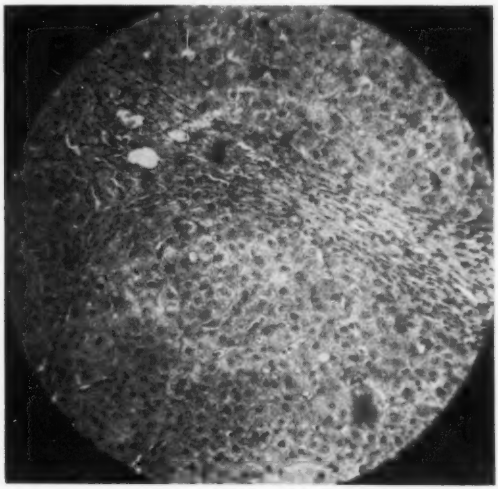

Fig. 4–Case 1 (Moderately advanced case). Fibrosis around portal tracts and lobules of the liver. (Hematoxylin and eosin. x350) Tissue removed during operation.

injected intramuscularly daily on three successive days preceding venography. On the day of investigation, the patient had a light breakfast. Half an hour before the procedure, 100 mg. of pethidine hydrochloride was injected intramuscularly.

The patient lay supine on the x-ray table and the upper limit of the spleen in the mid-axillary line was delineated by percussion. The spleen was enlarged in most cases and the organ was pushed up by the fluid in the peritoneal cavity so that the eighth intercostal space in the mid-axillary line was found to be the most suitable for introducing the lumbar puncture needle. The area was sterilized and then anesthetized as far as the splenic capsule with 5 to 7 ml.

TABLE II

MODERATELY ADVANCED CASES

Case No.	Name	Age	Sex	Hematemesis and/or melena	Veins in anterior abdominal wall	Ascites		Cachexia	Liver	Spleen	Blood				Date of Splenic Venography	Date of discharge from hospital or of death	Remarks
						Duration	Amount				T.P. gm.%	Alb. gm.%	Glob. gm.%	Bilirubin mg.%			
1	R.N.H.	16	M	+	+	3M	+++	+	N.P.	3F	7.1	2.6	4.5	3.0	1/15/54	7/24/54	Improved after splenectomy.
2	C.R.D.	26	M	+	+++	4M	+	+	1F, firm	4F	5.8	2.2	3.6	0.2	8/15/52	7/10/53	Death due to severe hematemesis and melena.
3	H.M.N.	40	M	−	+	3M	+++	+	1F, firm	3F	4.9	2.3	2.6	0.2	8/26/54	10/ 4 /54	Improved. Ascites has reappeared.
4	P.B.C.	38	M	−	+	1M	++	+	N.P.	N.P.	4.2	2.4	1.8	0.2	9/ 6 /54	10/ 5 /54	
5	S.M.B.	52	M	−	+	1M	++	+	N.P.	3F	5.8	4.0	1.8	1.3	3/20/53	3/28/53	Slight improvement. Had ascites when he left hospital.
6	H.L.R.	50	M	+	+	6M	++	+	N.P.	3F	5.7	2.2	3.5	1.0	5/28/54	6/29/54	Had slight ascites when he left hospital.
7	K.P.	45	M	−	+	1M	+++	+	N.P.	2F	4.4	2.0	2.4	0.1	12/ 7 /54	1/26/55	Marked improvement. No ascites.

− Absent
\+ Slight
++ Moderate
+++ Marked
M Month
Y Year
F Fingers below costal arch
N.P. Not palpable
T.P. Total protein

of 2 per cent procaine hydrochloride solution. In administering the anesthetic, the needle was introduced gradually and at each stage prior to the injection of the anesthetic, suction was exerted in the syringe to see if blood came into it. Blood in the syringe suggested that the spleen had most probably been pierced.

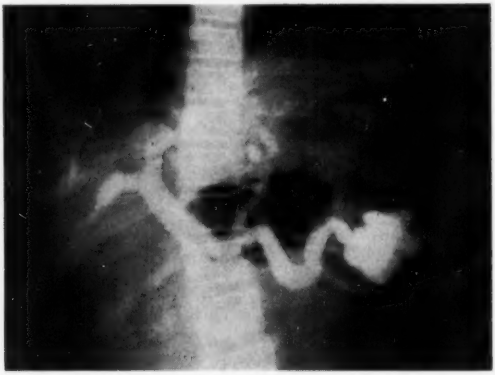

Fig. 5—Splenic venogram of Case 1 (Moderately advanced case). Intrahepatic branches of portal vein are faintly made out. The portal vein is dilated, the splenic vein is dilated and tortuous, and the gastric veins are prominently visualized.

The length of the imbedded needle gave a rough estimate of the distance the needle to be used for injecting the dye would have to be introduced to pierce the spleen.

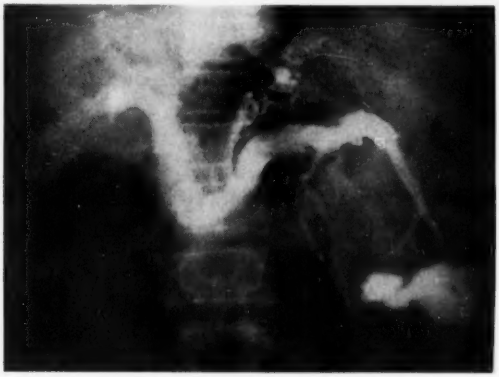

Fig. 6—Splenic venogram of case 5 (Moderately advanced case). The intrahepatic branches of the portal vein are not visualized, the portal and splenic veins are dilated, and the gastric and inferior mesenteric veins are visualized.

By using this technic, the chance of failure was much less than when we used to inject the radio-opaque dye blindly through the ninth intercostal space in the mid-axillary line.

Twenty ml. of 75 per cent aqueous solution of the disodium salt of N-methyl-3:5-diiodo-4-pyridone-2:6-dicarboxylic acid (Iodoxyl B.P.) was drawn into a 20 ml. Record syringe to which an adult size lumbar puncture needle was attached. The needle was introduced medially and slightly downwards through the anesthetized area for the required length and the dye was injected as quickly as possible. An x-ray was taken when 15 ml. of the dye had been injected. The needle was then taken out and the puncture point was sealed.

The patient was asked to hold his breath at the end of a deep inspiration from the time the needle was introduced until it was taken out. He was kept at bed rest for 24 hours and temperature, pulse, and respiration were charted every half hour. About four hours after the procedure the patient took a light meal.

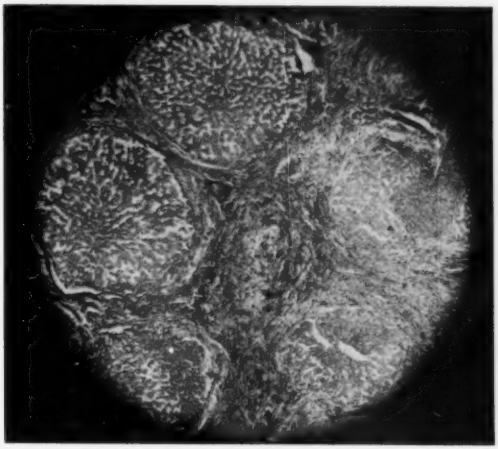

Fig. 7—Case 1 (Advanced case). Advanced portal cirrhosis of the liver. (Hematoxylin and eosin. x70). Tissue removed during operation.

In a normal splenic venogram, the splenic vein and the portal vein and its intrahepatic branches as far as the periphery of the liver are well visualized (Fig. 1).

The pathological changes observed in the liver tissue removed at operation or by needle biopsy, the portal venous pressure determined during operation in one of the small tributaries of the portal vein, and the changes observed in the splenic venograms of the patients with cirrhosis of the liver have been summarized in Tables IV, V and VI.

Comment

Twenty-seven patients with portal cirrhosis of the liver were studied. Attention was focused on the following points in splenic venograms: 1. visibility

TABLE III

ADVANCED CASES

Case No.	Name	Age	Sex	Hematemesis and/or melena	Veins in anterior abdominal wall	Ascites		Cachexia	Liver	Spleen	Blood				Date of Splenic Venography	Date of discharge from hospital or of death	Remarks
						Duration	Amount				T.P. gm.%	Alb. gm.%	Glob. gm.%	Bilirubin mg.%			
1	S.G.R.	11	M	+	+	1M	+	+	3F, very hard	3F	6.6	2.8	3.8	0.8	2/ 8 /54	5/30/54	Slight improvement. Splenectomy failed due to adhesion
2	N.C.S.	45	M	+	+	1½Y	+++	++	N.P.	3F	5.3	2.4	2.9	0.2	2/28/53	5/26/53	No improvement after ligation of hepatic and splenic arteries.
3	N.P.D.	39	M	+	+	10M	+++	+	1F, firm	3F	6.8	3.6	3.2	0.4	8/26/52	11/11/52	Died of hematemesis.
4	R.D.D.	48	M	+	+	1Y	++	+	N.P.	3F	5.4	2.2	3.2	1.0	12/ 6 /52	2/ 1 /53	Died of cholemia.
5	N.N.B.	50	M	−	++	9M	+++	++	1F, firm	3F	5.5	2.2	3.3	0.2	8/21/52	7/ 1 /53	Some improvement after ligation of hepatic and splenic arteries.
6	G.N.	24	M	+	+	1Y	+++	+	N.P.	2F	5.8	2.2	3.6	0.4	1/20/53	3/29/53	No improvement.

7	A.N.A.	33	M	+	+	4Y	++	+	N.P.	6F	3.8	1.4	2.4	1.5	1/4/54	1/26/54	Died of cholemia following an attack of infective hepatitis.
8	A.N.M.	40	M	−	+	1Y	+++	++	N.P.	3F	5.1	1.6	3.5	0.1	3/12/54	7/29/54	Moderate improvement.
9	A.N.S.	27	M	+	++	2M	+++	++	N.P.	3F	6.1	1.7	4.4	0.7	5/10/54	6/25/54	Died of cholemia precipitated by hematemesis.
10	M.I.	40	M	−	+	3M	+++	++	N.P.	2F	6.2	1.8	4.4	0.2	10/25/54	1/15/55	Some improvement. Had moderate ascites.
11	K.D.	35	F	−	++	3M	+++	++	N.P.	3F	6.4	2.7	3.7	0.4	11/10/54		Still in hospital. Slight improvement.
12	G.D.	28	F	−	+	3M	+++	++	N.P.	3F	6.4	2.2	4.2	0.2	10/29/54	12/15/54	Moderate improvement. Had slight ascites.
13	S.C.B.	28	M	+	+++	1½Y	+++	++	N.P.	3F	7.2	2.0	5.2	0.5	11/1/54	11/22/54	Died of cholemia precipitated by hematemesis.

− Absent
\+ Slight
++ Moderate
+++ Marked
M Month
Y Year
F Fingers below costal arch
N.P. Not palpable
T.P. Total protein

of intrahepatic branches of the portal vein; 2. dilatation and tortuosity of the splenic vein and dilatation of the extrahepatic portion of the portal vein and 3. visibility of gastric veins and of the inferior mesenteric vein.

1. Visibility of the intrahepatic branches of the portal vein:—These branches were not visible in 1 out of 7 early cases, in 4 out of 7 moderately advanced cases, or in 10 out of 13 advanced cases of cirrhosis of the liver. They were seen for some distance inside the liver but not as far as the periphery in 6 out of 7 early cases, in 3 out of 7 moderately advanced cases, and in 3 out of 13 advanced cases of cirrhosis of the liver. In no case of cirrhosis of the liver were the intrahepatic branches clearly seen as far as the periphery of the liver.

In cirrhosis of the liver there are obstructions to the portal venous radicles by fibrous tissue and distortion of hepatic architecture. These factors are most

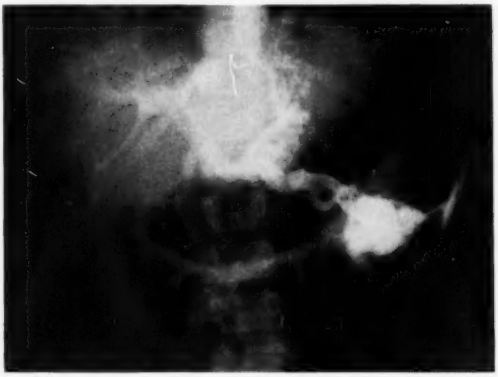

Fig. 8—Splenic venogram of case 1 (Advanced case). Intrahepatic branches are very thin and faintly made out. Inferior mesenteric and gastric veins are very prominently visualized.

probably responsible for the changes noted in the intrahepatic branches of the portal vein. As a rule, the more advanced the disease was, the less visible were the intrahepatic branches.

2. Dilatation and tortuosity of the splenic vein and dilatation of extrahepatic portion of the portal vein:—These changes were present in all the 27 patients, except one in whom the portal vein alone was affected. These abnormalities are due to the portal hypertension present in cirrhosis of the liver.

3. Visibility of gastric veins and of the inferior mesenteric vein:—Of 7 early cases of cirrhosis of the liver, the gastric veins were visualized in the venograms of 3 and there was a history of gastrointestinal bleeding in 2; of 7 moderately advanced cases, the gastric veins were visible in 5, and there was a history of bleeding in 3; of 13 advanced cases, the gastric veins were visible in 10 and there was a history of bleeding in 8.

TABLE IV

EARLY CASES

Case No.	Name	Changes in liver tissue removed by needle biopsy or at operation	Portal venous pressure in mm. of saline	Splenic venography							History of hematemesis or melena
				Intrahepatic branches of portal vein		Dilatation of splenic vein	Tortuosity of splenic vein	Dilatation of portal vein	Visualization of gastric veins	Visualization of inferior mesenteric veins	
				Not visible	Visible for short distance inside liver but not as far as the periphery						
1	S.L.P.	Proliferation of bile ducts and early fibrosis (Fig. 2)	–		+ (Fig. 3)	+	+	+	+	–	–
2	P.C.P.	–	–		+	+	++	++	+++	+	+
3	N.C.B.	Fatty infiltration in peripheral part of lobule and periportal fibrosis	340	+		+	+	+	+	+++	+
4	K.C.M.	Periportal round cell infiltration and early fibrosis	–		+	++	++	++	–	–	–
5	N.B.B.	Fatty infiltration and early fibrosis	–		+	+	++	+	–	–	–
6	S.C.M.	–	–		+	+	+	+	–	+	–
7	B.K.M.	Postnecrotic scarring	–		+	–	–	+	–	–	–

– Not done, or absent
+ Slight
++ Moderate
+++ Marked

Of the 27 patients, a history of gastrointestinal bleeding was present in 13 and the gastric veins were visible in the venograms of 18. There was only one patient in whose splenic venogram the gastric veins were not visible though he had given a history of hematemesis, a repetition of which later proved fatal. In 6 patients, though the gastric veins were visible in the splenic venogram, there was no history of gastrointestinal bleeding.

The inferior mesenteric vein was visible in 12 of the 27 patients.

Portal hypertension, which is present in cirrhosis of the liver, makes the gastric veins and the inferior mesenteric vein visible in a splenic venogram and the prominence of the collaterial veins is a measure of the degree of

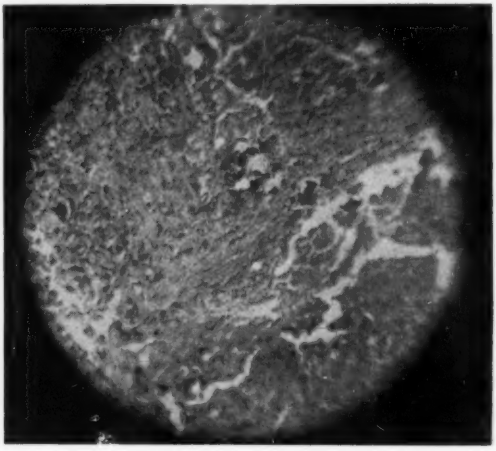

Fig. 9—Case 3 (Advanced case). Advanced portal cirrhosis of the liver. (Hematoxylin and eosin. x350) Tissue removed by needle biopsy.

hypertension. There was a definite correlation between gastrointestinal bleeding and visibility of gastric veins in a venogram.

Cirrhosis of the liver is usually diagnosed on clinical grounds. Liver function tests, as the name implies, give an idea of functional capacity of the liver but not of the pathological processes in the organ. Needle biopsy of the liver has its place in the confirmation of the diagnosis, but it has its limitations also. It may be difficult to get proper and sufficient material when the liver is hard and small and there is ascites. There is not always a correlation between the pathological changes noted in the tiny bit of liver tissue obtained by needle biopsy and the clinical condition of the patient. Further, liver biopsy gives very little information on the portal venous tree and none on the collateral veins, thus it will give no information on the presence or degree of portal hypertension.

TABLE V

MODERATELY ADVANCED CASES

Case No.	Name	Changes in liver tissue removed by needle biopsy or at operation	Portal venous pressure in mm. of saline	Splenic venography							History of hematemesis or melena
				Intrahepatic branches of portal vein		Dilatation of splenic vein	Tortuosity of splenic vein	Dilatation of portal vein	Visualization of gastric veins	Visualization of inferior mesenteric veins	
				Not visible	Visible for short distance inside liver but not as far as the periphery						
1	R.N.H.	Portal cirrhosis (Fig. 4)	400		+ (Fig. 5)	+	+	+	++	−	+
2	C.R.D.	Portal cirrhosis	350	+		++	++	++	+	+	+
3	H.M.N.	−	−		+	+	+	++	−	−	−
4	P.B.C.	−	−		+	+	+	++	++	+	−
5	S.M.B.	−	−	+ (Fig. 6)		++	+	++	++	+	−
6	H.L.R.	Loss of hepatic structure, fibrosis and regeneration at places	−	+		+	+	+	++	−	+
7	K.P.	Fatty infiltration and early fibrosis	−	+		+	+	+	−	+	−

− Not done, or absent
\+ Slight
++ Moderate
+++ Marked

TABLE VI

ADVANCED CASES

Case No.	Name	Changes in liver tissue removed by needle biopsy or at operation	Portal venous pressure in mm. of saline	Splenic venography							History of hematemesis or melena
				Intrahepatic branches of portal vein		Dilatation of splenic vein	Tortuosity of splenic vein	Dilatation of portal vein	Visualization of gastric veins	Visualization of inferior mesenteric veins	
				Not visible	Visible for short distance inside liver but not as far as the periphery						
1	S.G.R.	Advanced portal cirrhosis. (Fig. 7)	360		+ (Fig. 8)	+	+	+	+++	++	+
2	N.C.S.	Periportal round cell infiltration and early fibrosis	290		+	+	−	+	++	−	+
3	N.P.D.	Advanced portal cirrhosis. (Fig. 9)	−	+ (Fig. 10)		++	++	++	−	−	+
4	R.D.D.	−	−	+		++	++	+	+	−	+
5	N.N.B.	Fatty changes, regenerating nodules and periportal fibrosis	300	+		+++	+	++	−	−	−

6	G.N.	–	–	+		++	++	+	+	–	+
7	A.N.A.	–	–	+		++	++	+	+	–	+
8	A.N.M.	Fatty infiltration and periportal fibrosis	–	+		++	++	++	+	–	–
9	A.N.S.	Fatty infiltration, periportal fibrosis and regeneration at places	–	+		++	++	++	+	++	+
10	M.I.	Portal cirrhosis	–	+		+	+	+	–	–	–
11	K.D.	Regenerating liver cells and periportal fibrosis	–	+		+	+	+	++	+	–
12	G.D.	Portal cirrhosis	–		+	+	+	+	++	++	–
13	S.C.B.	–	–	+		+	+	+	+	+	+

– Not done, or absent ++ Moderate
+ Slight +++ Marked

Splenic venography gives an idea of the condition of the portal venous tree and of the degree of portal hypertension. If the gastric veins are visible in a splenic venogram, there is always the possibility of gastrointestinal bleeding.

We have carried out splenic venography on more than 60 occasions in different types of cases. Except for some local pain and tenderness and an occasional rise in temperature, there have been no untoward incidents. These minor complications usually disappear within two to three days. The procedure is simple and the results are obtained immediately after the examination.

From the consistent results obtained in the patients studied, it is suggested that splenic venography is a valuable method of investigation in the diagnosis of cirrhosis of the liver, in establishing the stage of the disease, and in assessing the degree of portal hypertension.

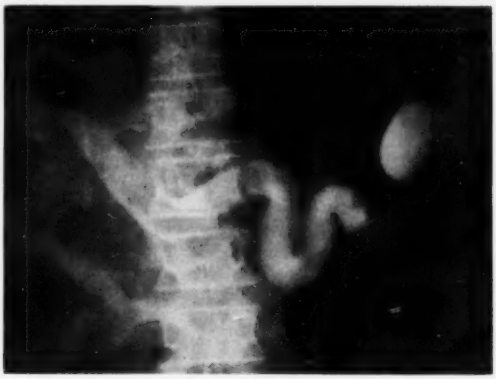

Fig. 10—Splenic venogram of case 3 (Advanced case). Intrahepatic branches of the portal vein are not visualized. The portal vein is dilated and splenic vein is dilated and tortuous.

Summary

Splenic venography was carried out in 27 patients with portal cirrhosis of the liver.

The intrahepatic branches of the portal vein were either not at all visualized in the venograms or were seen for only a short distance inside the liver. As a rule, the more advanced the disease, the less visible the branches.

The splenic vein was dilated and tortuous and the extrahepatic portion of the portal vein was dilated in almost all the patients.

The gastric veins and the inferior mesenteric vein were often visualized in the splenic venograms. There was a definite correlation between the history

of hematemesis and/or melena and visualization of the gastric veins. In patients in whose splenic venograms the gastric veins were visualized, the incidence of gastrointestinal bleeding was always higher.

Advantages of splenic venography over liver biopsy in the investigation of portal cirrhosis of the liver are discussed.

ACKNOWLEDGEMENTS

We are grateful to Dr. A. K. Dutta Gupta, Principal and Superintendent, Nilratan Sircar Medical College and Hospitals for giving us the facilities for this work and to Professor S. B. Bose, Professor of Radiology, Dr. R. Roy Chaudhury, Assistant Radiologist, Professor S. N. De, Professor of Pathology, and to Professor S. Sarker, Professor of Biochemistry for their help in the various investigations. Our thanks are due to Mr. M. Mazumder, artist, for the photomicrographs. It is gratefully acknowledged that Dr. A. N. Sen Gupta, House Physician to Associate Professor of Medicine cooperated in the earlier part of the investigation.

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NONSPECIFIC GRANULOMATOUS DISEASE OF THE RECTUM FOLLOWING REGIONAL ILEITIS*

Case Report

FREDERICK VOGEL, M.D.†

New York, N. Y.

This is the case report of a 28-year old, single female of Romanic extraction. In reporting a case fascinating to us we are frequently liable to divorce the disease from the living patient. In this case it should be mentioned that this young lady was of almost angelic appearance, strictly brought up, always in her mother's company, even in the examining room. She was initially observed by me in 1946 when she gave the following history: In 1944 at 18 years of age she was operated on for bilateral "cryptitis and *condylomata acuminata*". The pathological report of nonspecific granulomatous growth containing giant cells was made on the excised tissue. This report was not known to me until many years later. Frei and Wassermann tests were negative. One month later she had more condylomata which were cauterized in a doctor's office. Shortly thereafter there was a septicemia with *streptococcus viridans* found in blood culture. Also in 1944 she had an appendectomy for a supposedly acute appendicitis. This is an important feature of the history. No reference was made to any pathology of the ileum at this operation. Her chest and sputum were negative for tuberculosis.

In May 1946 she consulted me for rectal pain and discharge of some six months' duration. Examination showed an acute proctitis with small anal fissures, enlarged papillae and a small blind external fistula. Sigmoidoscopy revealed proctitis with pseudomembraneous patches of the rectal mucosa. Digital examination did not reveal any mass or obstruction; there was tenderness of the anal area. Rectal smear, surprisingly enough, showed numerous bacteria, among them gonococci and numerous spermatozoa. Sexual intercourse was vigorously denied. Under penicillin and local rectal irrigations her condition improved somewhat, but in six months she returned with essentially the same complaint and the same findings on examination as previously described. Frei test at this time was again negative. The patient refused surgery and was not seen again until seven years later.

In the meantime the following had occurred: Three months after her last visit there were daily diarrheas and there was general malaise, abdominal pain, anorexia, and the patient took a down-hill course. In January 1950 she was taken to Memorial Hospital where a right colectomy and resection of the lower

*Presented at the meeting of the New York Proctologic Society on April 14, 1955.

†From the Proctologic Department of the New York Polyclinic Medical School and Hospital, New York, N. Y.

23 cm. of ileum was done. The disease was principally in the lower ileum but also involved the ascending colon and the right tube, both of which were also removed. The diagnosis was: Typical regional ileitis. After this the patient made a rapid and complete recovery. She returned to work as secretary and felt well until May of 1954, when she returned to me with the complaint of rectal pain for the past four days occurring during evacuation and followed by backache lasting an hour. There were six to seven evacuations a day. At the same time she noted some discharge from the vagina. Inspection revealed the perianal

Fig. 1–Specimen obtained by surgery of the chronic ileitis. Fibrosis, granulomatous tissue.

area to be edematous posteriorly and bilaterally and there was inflammatory infiltration. There was a granulomatous sentinel pile hiding a fissure of the posterior commissure. Yet there was hardly any sphincter spasm; on digital examination there were irregular granulomatous masses encircling the entire anal and lower rectal canal up to about 7½ cm. from the anal verge. Within this mass three individual strictures could be differentiated, of which the uppermost one scarcely admitted a finger tip. In the rectovaginal septum, there was an egg-sized area of induration with fluctuation. Pressure on this abscess produced pus and blood from the vulva. The patient was very resistant to vaginal explo-

ration, and when she eventually agreed to it, a granulomatous fistulous opening was found and probed in the distal and posterior portion of the vagina, therefore establishing a rectovaginal fistula.

Thereupon the patient was admitted to the Polyclinic Hospital for further study. A sigmoidoscopy was performed with a narrow caliber scope and a granular constricting mass was seen; it was dark brownish-red and bled easily on touch. Beyond this area the mucous membrane was, and still is, perfectly normal. Frei test was done again twice in succession, but still remained negative

Fig. 2—Biopsy from rectal lesion: fibrosis with granulomatous tissue. Arrow indicates area from which large magnification shows granuloma (Fig. 3).

as before; so was Wassermann. There was moderate secondary anemia. Cultures were taken from the vagina and the rectal discharge; each failed to suggest any specific agent. Biopsy was taken from three different sites of the anorectal lesion and the histologic report was: Nonspecific granulomatous inflammatory tissue. The slides should unequivocally show the identity with the report on the ileocolonic specimen removed by surgery four years ago at Memorial Hospital. Unfortunately, the slide of the specimen ten years ago could not be made available.

Treatment:—Not knowing the etiology of a disease leaves therapy open to experiment and empirical guessing. In our case, considering the broad therapeutic spectrum on virus and bacteria alike, we have switched to Aureomycin and Achromycin supported by sulfathalidine after, but little result was accomplished with penicillin and streptomycin. We realized that at least the secondary flora will be affected, not knowing whether the basic disease is infectious. The result was good. Although the local anorectal lesion changed little, there was less discharge and less distress. The patient regained her strength and appetite and

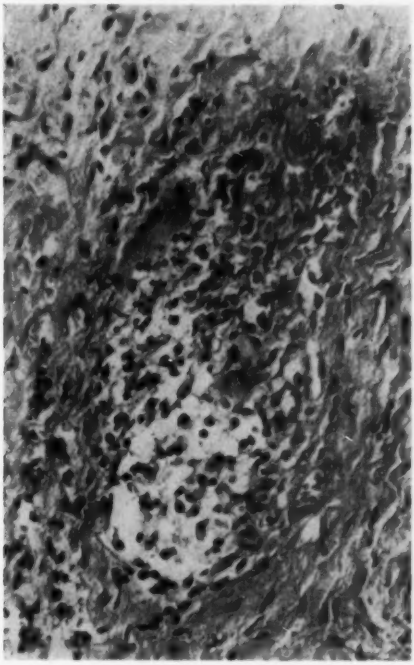

Fig. 3—Large magnification of area pointed out in Figure 2. Granuloma containing giant cells. Biopsy from rectum.

weight. After a few weeks she felt well and looked well and was able to resume her work. We may deduct that we have treated a systemic disease rather than a localized lesion.

The prognosis is guarded. Textbooks tell that this disease distinguishes itself from tuberculous granuloma by its tendency to regression without scar formation. On the other hand, we have seen in our case relapse after intervals of temporary improvement lasting years. Great caution is therefore indicated in risking a prognosis. If the case should take a turn for the worse with complete

occlusion of the anorectal lumen, only a colostomy could save the patient's life, and who knows for how long.

Rectal involvement of the condition diagnosed as regional ileitis is very uncommon. This fact is stressed by many authors. Crohn in his monograph on Regional Ileitis does not report observation of any case, neither is it mentioned in the textbooks of Bacon and Gabriel. As far as I have been able to gather from the literature, only three similar cases have been reported. But none of their histories and course was as involved as ours, which may give rise to pondering about the real nature of this disease and the possible virus-bacteria relation if it is based on an infection at all. If a virus is the causative agent and possibly a relative of the Nicolas-Favre disease or of *condylomata acuminata*, which had been present before in this patient, the question arises, whether it invades a system previously weakened by bacteria, or is it vice versa, with abscess and/or fistula formation first?

Summary

A case of anorectal involvement with granulomatous disease diagnosed as nonspecific chronic ileitis has been presented. The case has an involved history which may give rise to ponder about a possible infectious basis of this disease and the interrelation of virus and bacteria, either one of which may be primary or secondary. Only three actual similar cases have been reported in the literature. Therefore this presentation.

Addendum

A few months after this report was written the patient developed a left-side ischiorectal abscess which was hot-red and was incised. In the course of the after-care a fistula was forming, which could be probed about an inch and a half posteriorly towards the posterior commissure and about an inch anteriorly. Despite all efforts to keep saucerization open for drainage, the fistula formed and fluid, syringed into the external ischiorectal opening, escaped through the vagina, therefore establishing an ischiorectal vaginal fistula.

Pathology of Granulomatous Disease

General:—Granuloma formation is possibly a protective device whose function is to isolate substance from the body tissues. Granuloma formation is a reaction of tissue acted upon by an irritant of lower intensity. As a response to this irritant cells pile up which are released from either the blood stream (lymphocytes, etc.) or from wandering tissue cells which are alternately called histiocytes, mononuclears and macrophages. But the only cell which proliferates is the fibroblast.

The fibroblast replaces the special cell of an organ which had been destroyed by the irritant. The result may be a cellular fibrous tissue. If, however,

the fibroblasts do not multiply but excrete collagen fibres, they form dense acellular fibrous connective tissue. This happens in chronic inflammation if the irritation subsides. Fibrosis is divided into two great groups, the productive fibrosis and the replacement fibrosis.

If the histiocytes become swollen and contain lipoid, they are referred to as epithelioid cells. These fuse to form giant cells which are characteristic of all chronic granulomata. The accumulation of cells may be so great as to form a tumor-like swelling. Therefore, the term "productive inflammation".

The infectious granulomata form a special group. They are commonly known due to tuberculosis, lues, lepra, mycoses, amebiasis, *lymphogranuloma venereum*, and *schistosomiasis japonicum*. Foreign bodies are regarded as nonspecific irritants; the granuloma of chronic ileitis is also called nonspecific because its irritant has remained unveiled so far. The same goes for Boeck's sarcoidosis. Both lesions offer identical histopathology like tuberculosis, but they show clinical varieties, never caseous necrosis and—most important—Koch bacilli have never been obtained from them. Also Hodgkins' granuloma was termed tuberculous by Karl Sternberg who changed his mind later on.

Specific:—Chronic ileitis or enteritis has been described as a progressive lymphangitis affecting and sclerosing the lacteal vessels in the intestinal *lamina propria* immediately underneath the epithelium of the intestinal glands, extending into the submucosa, muscularis, and subserosa. As a result there is elephantiasis of the intestinal wall, the mesentery and the regional lymph glands. The endothelial lining of the lymphatics proliferates and desquamates leading to mechanical obstruction of the lymphatic flow. Additional proliferation of mesenchymal cells and infiltration by lymphocytes and monocytes form the granuloma. Interference with the blood supply due to pressure may cause ulceration of the mucosa which was originally unaffected but has secondarily thickened. The peristalsis may be impaired by involvement of the perineural lymphatics thus causing constipation. It is said that there is a tendency to regression without scarring or caseation in contrast to tuberculosis. The microscopic similarity of the lesion, however, gave rise to speculation that chronic ileitis may be due to an attenuated or bovine strain of tubercle bacillus.

Many other bacteria have been mentioned as possible causative organs, among them streptococcus viridans, the germ which had caused a septicemia in our patient at the onset of her disease.

The predominant presumption, however, is infection with a virus possibly related to *lymphogranuloma venereum;* this speculation was supposedly bolstered by the fact that antiviral therapy, e.g., aureomycin or terramycin has shown the only beneficial effect. This is problematic, however, as there is no unequivocal evidence of such effect on virus, which is questioned by some experienced men.

Allergy as cause of granulomatous disease is another hypothesis, e.g., eosinophylic granuloma or periarteritis nodosa.

Clinically, there may be a prodromal stage consisting of anorectal abscesses and fistula formation. This may long precede diarrhea. Also appendicitis had been present in more than 30 per cent of the cases. Diarrhea begins with occasional spells gradually becoming more severe. There are abdominal cramps, there is nervousness, weakness, dull sacral pain, general malaise and constipation. An occasional low grade temperature goes along with a moderate rise of leucocyte count and a moderate anemia. This may develop over the course of years. In women the menstruation remains regular contrasting ulcerative colitis. Symptoms of obstruction are rare. Multiple rectal fistulae divide it from Boeck's sarcoid, so does the roentgenographic string-sign.

This fistula formation is said to be due to leakage from the diseased segment of proteolytic material which seeps through the pelvis and retroperitoneal fat along the levator ani fascia entering the rectal canal above the sphincter muscles. There may be involvement of the ischiorectal fossa. Other possible complications are hemorrhage and perforation.

It has been stressed that the rectum and the sigmoid are rarely invaded with this small intestine disease which, if caudally progressive, may invade the most proximal colon. In the literature of the past 15 years there are only three cases. It is so uncommon that it remains unmentioned in Crohn's monography and in the textbooks of Bacon and Gabriel.

Anorectal malignancy must be considered in differential diagnosis.

President's Message

I thought the Fellows of the College would be interested in an interim report on the status of our College.

Our total membership at December 1, 1955, was 833. This included 26 Honorary Fellows; 30 Life Fellows; 311 Fellows; 154 Associate Fellows and 312 Members. Dr. Lynn A. Ferguson has been unanimously selected by the Executive Committee to serve as your Acting Secretary-General until October, 1956. Definite action on the affiliation of local groups is planned for the April meeting of the Board of Trustees in New Orleans.

The Research Committee recommends an annual prize of $500.00 for the best paper on gastroenterology presented by an interne, a resident or a fellow. This prize will be publicized in the medical journals and through the medical schools and hospitals.

The Program Committee has planned panel discussions to occupy 1½ hours of each of the six scientific sessions at the next Convention. The six medical schools in New York City will each sponsor one of these panel discussions.

I. T. Nif

NEWS NOTES

1956 Ames Awards Contest of The American College of Gastroenterology

The American College of Gastroenterology, in cooperation with the Ames Company of Elkhart, Indiana, again takes pleasure in announcing the 1956 Ames Award Contest for the best papers in Gastroenterology.

There will be two classes of awards as follows:

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First Prize—$500.00, a certificate of merit and a 1 year subscription to The American Journal of Gastroenterology, official publication of the American College of Gastroenterology.

Second Prize—$250.00, a certificate of merit and a 1 year subscription to The American Journal of Gastroenterology.

Best Paper Published

For the best paper published in The American Journal of Gastroenterology, during the twelve months ending 30 June 1956, for which no prize has been previously awarded, $250.00.

Rules and Regulations

All papers submitted must represent original work in Gastroenterology, must not have been previously published except for abstracts or short preliminary reports and must not have been previously presented at any National meetings.

The contents of the papers can be clinical or basic science. Clinical papers must not be case records, but controlled clinical work.

The length of a paper is no criterion for originality or value.

All entries for the 1956 prizes, with the exception of those already published in The American Journal of Gastroenterology, must be typewritten in English, double-spaced on one side of the paper and submitted in six copies.

The winning entries will be selected by the Research Committee of the American College of Gastroenterology and the awards will be made at the Annual Convention Banquet of the College, to be held in New York in October 1956.

All papers selected for awards become the property of the American College of Gastroenterology and the decision of the judges will be final. Should

none of these papers submitted meet the standards set by the Committee, the Committee, reserves the right to withhold the making of any award.

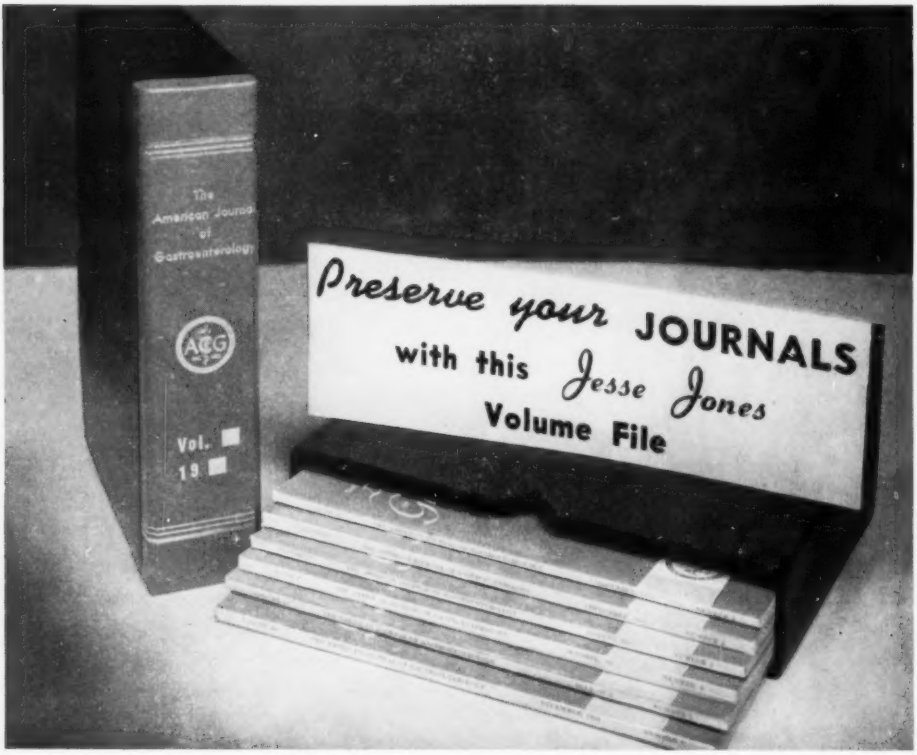
The recipient of the first prize will present the paper in person at the Annual Meeting of the College.

All unpublished entries must be received not later than 15 July 1956 and should be addressed to the Research Committee, American College of Gastroenterology, 33 West 60th St., New York 23, N. Y.

American Gastroscopic Society

The annual meeting of the American Gastroscopic Society will be held on 10, 11 June 1956 at the Knickerbocker Hotel, Chicago, Ill.

Further information may be obtained by writing to: Dr. C. Wilmer Wirts, Secretary-Treasurer, 1025 Walnut St., Philadelphia 7, Pa.



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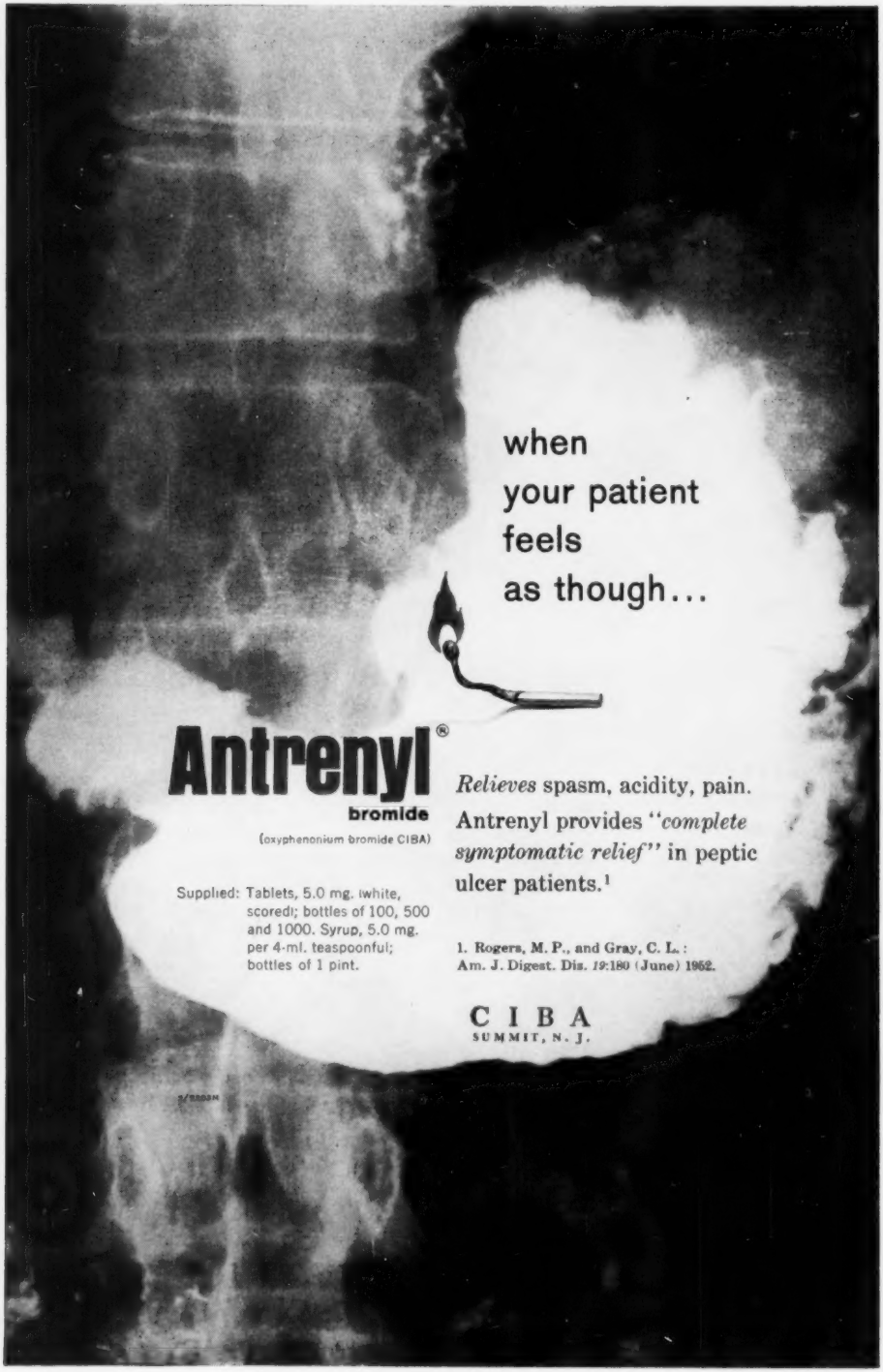
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1. Rogers, M. P., and Gray, C. L.: Am. J. Digest. Dis. *19*:180 (June) 1962.
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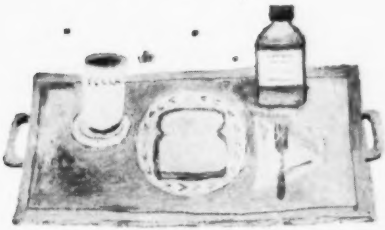

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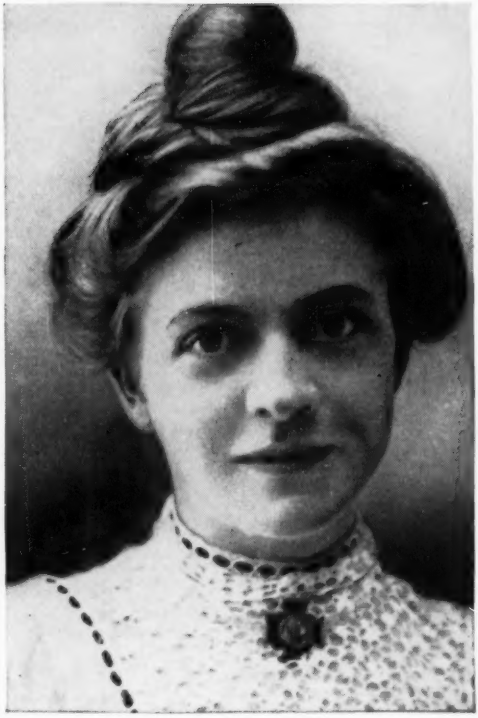

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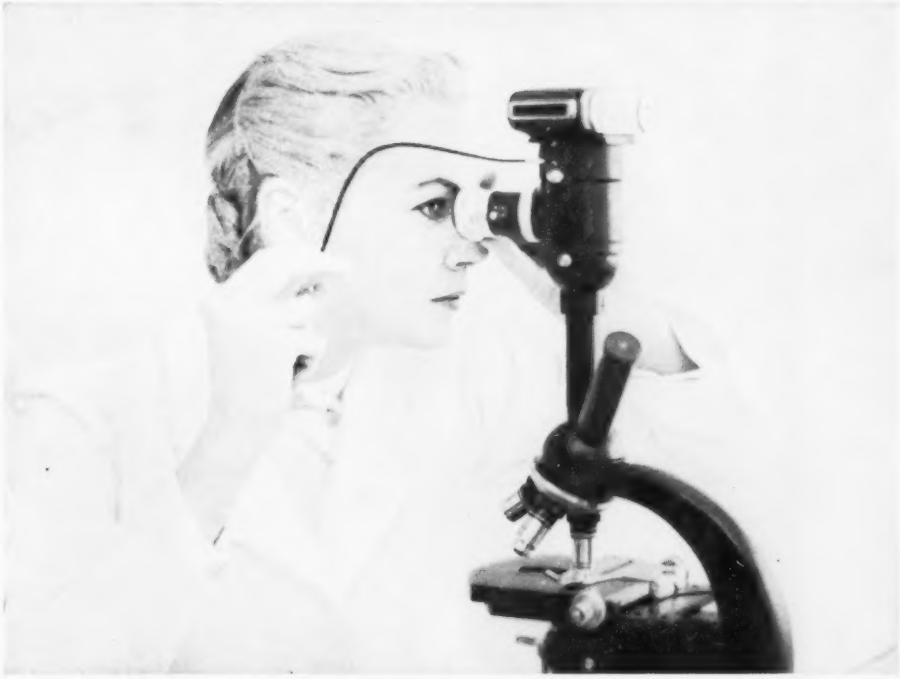

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SULFATHALIDINE favors early healing. It is virtually nontoxic.

SULFATHALIDINE is also an important adjuvant to the treatment of ulcerative colitis.

Dosage depends on body weight. The average adult dose is 8 to 12 tablets (each 0.5 *Gm.*) daily in divided doses. 'Sulfathalidine' can also be given as the pleasantly-flavored suspension, CREMOTHALIDINE, each oz. containing 6.0 *Gm.* of 'Sulfathalidine.'

References: 1. N.N.R. 1954, p. 107. 2. J.A.M.A. 153:1516 (Dec. 26) 1953.

SHARP & DOHME

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pronounced

MUSCLE-RELAXING ACTION

= Equanil*

MEPROBAMATE (2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate)

LICENSED UNDER U.S. PATENT NO. 2,724,720

For significant relief in myositis, osteoarthritis, backstrain, and related conditions marked by:

- ***Muscle spasm***
- ***Stiffness and tenderness***
- ***Restriction of motion***
- ***Pain***

As a superior muscle-relaxant, EQUANIL offers predictable action and full effectiveness on oral administration. It does not disturb autonomic function and is relatively free from gastric and other significant side-effects. Its anti-anxiety property provides important correlative value.

Usual dosage: 1 tablet t.i.d. The dose may be adjusted either up or down, according to the clinical response of the patient.

Supplied: Tablets, 400 mg., bottles of 50.

Wyeth®
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anti-anxiety factor
with muscle-relaxing action
. . . relieves tension

*TRADEMARK

to NORMALIZE, use KONSYL®

It is important, when inducing normal bowel function, to supply a non-irriating bulk to the colon, especially in those cases in which it has been necessary to eliminate from the diet the high roughage foods containing irritating bulk (lignin and cellulose).

It has been shown[1] that the colon resumes a more normal peristaltic pattern[2] when it is supplied with a stool of medium soft consistency of sufficient bulk[3], especially if the indigestible portion of that bulk consists primarily of hemicellulose[4].

KONSYL is a vegetable concentrate of naturally occurring hemicelluloses. It is derived from blond psyllium seed and provides just the moist, smooth, effective bulk so essential to normal peristalsis. Its use has been shown to materially hasten the rate of improvement in patients with the irritable colon syndrome[5]. KONSYL contains 100% bulk producing material.

Furthermore, Konsyl is available in 6-ounce and 12-ounce containers at significantly lower-cost-to-patient prices. That's why we say

to NORMALIZE, use KONSYL®

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3. Wozasek, D., & Steigman, F., Am. J. Digest. Dis., 9:423, 1942
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5. Lieberthal, M. M., Conn. State M. J., 19:86, 1955

FORMULA: KONSYL CONTAINS 100% PLATAGO OVATA COATING.

Made by BURTON, PARSONS & COMPANY *Since 1932*

Originators of Fine Hydrophilic Colloids

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sugar and spice and . . . gastric hyperacidity

Nice to taste . . . difficult to digest . . . the result, more often than not, will be gastric hyperacidity. Bad experiences and good intentions notwithstanding, this particular chain of misfortune is likely to recur. With Gelusil, however, excessive gastric acidity — whether acute or chronic — can be quickly and pleasantly relieved.

Sustained antacid action: The sustained action of magnesium trisilicate and specially prepared aluminum hydroxide gel restores and maintains a mildly acid gastric pH, without over-neutralizing or alkalizing. Gelusil thus avoids the twin dangers of acid rebound and systemic alkalosis.

Non-constipating: Gelusil's aluminum hydroxide component assures a low aluminum ion concentration; hence the formation of astringent — and constipating — aluminum chloride is minimal.

Dosage: 2 tablets or 2 teaspoonfuls two hours after eating or when symptoms are pronounced. Each tablet or teaspoonful provides: 7½ gr. magnesium trisilicate and 4 gr. aluminum hydroxide gel.

Gelusil®

ANTACID • ADSORBENT

WARNER-CHILCOTT